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Flow velocity measurement in haemodialysis access using 4D MRI

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DECLARATION

I, Dr. Jennifer Downs, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise), and that neither the whole work or any part of it has been, is being or is to be submitted for another degree in this or any other university.

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14 August 2016

ABSTRACT

Flow velocity measurement in haemodialysis access using 4D MRI

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Treatment of renal failure while awaiting transplant requires vascular access, which comes with both complications and failure rates. In order to improve this, information about the AVF or AVG itself, as well as the haemodynamics is required. This data will then be used for computer modelling techniques and computational flow dynamics. Previously, the required imaging was provided by contrasted MRI, contraindicated in renal failure. Haemodynamic data was prvided by, amongst other things, duplex Doppler. New MRI software that provides imaging data as well as haemodynamic information without using contrast could be used to provide new high-quality data for modelling.

Methods: This was a prospective pilot study. Six control cases (with no history of vascular illness or surgery of any kind to the right upper arm), as well as three grafts and five fistulae underwent phase contrast MR angiography of the right upper arm with a Siemens Magnetom Symphony 1.5T MRI Scanner. Images were then processed using Supertool in Matlab, and flow velocities at predetermined points on the brachial artery and cephalic vein, graft and fistula were calculated.

Results: Velocities ranged from 5.8 cm/sec in a volunteer's brachial artery to 85.5 cm/sec in an arteriovenous fistula patient's brachial artery. Flow volumes in the cephalic vein or access varied from 6.9 ml/min. in a volunteer and up to 4398.1 ml/min. in an arteriovenous fistula. Graphical representations show marked haemodynamic changes throughout the imaged vessels.

Conclusion: This technique provides good imaging and quantitative data about small vessel haemodynamics.

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- The staff of the Groote Schuur chronic haemodialysis unit and Groote Schuur MRI unit.

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ABBREVIATIONS

CKD	Chronic kidney disease
ESRD	End-stage renal disease
RRT	Renal replacement therapy
USA	United States of America
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
MRI	Magnetic resonance imaging
NKF-DOQI	National Kidney Foundation–Dialysis Outcomes Quality Initiative
FFBI	Fistula First Breakthrough Initiative
CIMINO	Care improvement by multidisciplinary approach for increase of native vascular access obtainment
PTFE	Polytetrafluoroethylene
DSA	Digital subtraction angiogram
CT	Computerised tomography
MRA	Magnetic resonance angiography
CTA	Computerised tomography angiogram
2D	Two-dimensional
3D	Three-dimensional
4D	Four-dimensional
Pmp	Per million population
PSV	Peak systolic velocity

CHAPTER 1
PROPOSAL

1.1 Introduction

The incidence of renal failure in sub-Saharan Africa is increasing. The treatment of end-stage renal disease (ESRD), while including managing causative diseases and complications of the ESRD, requires renal replacement therapy (RRT). Quite clearly, the ideal way to do this is via renal transplant. The other way to provide this is via dialysis to perform some functions of the failed kidney. This can be provided by two methods: machines performing the filtration function of the kidney on blood circulated through them (haemodialysis), or peritoneal dialysis, where the patient's peritoneal membrane acts as a filter to remove dialysates from the blood.

Although efforts are being made to minimise time on haemodialysis programmes and improve access to transplants, the current reality is that the average patient can spend (depending on various factors) months to several years on haemodialysis. In order for haemodialysis to take place, vascular access is required. This access must be safe, cause minimal complications, and not require repeated procedures for the patient. Currently, this is provided by the arteriovenous fistula (AVF) or arteriovenous graft (AVG) for haemodialysis access. These are generally peripheral procedures, placed most often in the upper limb, and allow a sufficiently high blood flow rate in a smaller peripheral vessel, which allow adequate haemodialysis to take place. They are, however, not without complications of their own. The most important of these is failure of the access itself. As each patient has only limited sites suitable for AVF or AVG creation (because of patient anatomy and complications from previous lines and procedures), every attempt should be made to make each access AVF or AVG the last one for that patient.

In order to optimise the performance of the access, information about the AVF or AVG itself, as well as the haemodynamics of the flow through the access, is required. Once this information is gathered, it could then be applied to see if alterations in technique or materials would improve patency rates, decrease maturation times, and decrease complications.

1.2 Background

Haemodialysis is the movement of water and solutes across a semipermeable membrane, using diffusion and convection, out of the patient's circulatory system. Diffusion is the movement of solutes across a semipermeable membrane along a concentration gradient. Clearance of a solute via diffusion is dependent on many things – molecular weight, electrical charge, fluid concentration gradient, type of membrane, and blood and fluid flow rates. Convection refers to the movement of solvent and dissolved solutes across a semipermeable membrane along a hydrostatic pressure gradient. Ultrafiltration is the convective movement of water across the semipermeable membrane.

Haemodialysis combines these principles to clear the patient's blood of toxic waste products. The blood travels via an extracorporeal circuit – from patient via access, into the "arterial side" of the circuit. It flows through a pressure monitor, and heparin is added. It then enters the dialysis machine. This machine consists of a semipermeable membrane with two different fluid circuits flowing in opposite directions on either side: blood and dialysis fluid (machine characteristics differ in terms of membrane type, surface area, permeability characteristics and other components). The blood then leaves the dialysis machine and enters the "venous side" of the circuit. This flows through a pressure monitor and clamp mechanism (in case of sudden failure of the machine to stop blood from flowing out) and back into the so-called venous needle in the vascular access. The volume of fluid filtered off is regulated by the machine dictating flow rates of the dialysis fluid[1]. Different types of haemodialysis make use of varying levels of diffusion, convection and ultrafiltration, depending on the setting of the patient who requires dialysis. However, they all require a minimum flow rate of blood into the machine of 300–500 ml per minute.

In the short term, this can be provided by indwelling catheters in the central venous system. However, in the case of long-term dialysis, provision must be made to get permanent access to this high blood flow rate, all the while minimising trauma and complications.

1.3 Literature review

In the western world, chronic kidney disease (CKD) and end-stage renal disease (ESRD) are increasingly prevalent. CKD is the ninth leading cause of death in the USA[1]. In 2005, 106 000 patients began treatment for ESRD, and ESRD consumed 6% of the Medicaid budget for that year. Many of the costs were associated with the transition onto ESRD therapy, such as catheters, vascular access procedures, failed access and the complications of the above treatments[1].

Eighty percent of the world's population on renal replacement therapy (RRT) is in North America, Europe and Japan, comprising only 15% of the world's population[2]. In sub-Saharan Africa, data is obviously more difficult to come by, but the mortality rate from ESRD is obviously much higher[2]. With the expected explosion of hypertension and diabetes in sub-Saharan Africa (130% by 2020), and the increasing burden of HIV-associated nephropathy, and therefore downstream increases in CKD and ESRD[2], all efforts to improve and streamline management of this condition should be made.

Management of ESRD requires provision of RRT while the patient is awaiting renal transplant. This can be provided in two forms: continuous ambulatory peritoneal dialysis, and haemodialysis. Haemodialysis requires the passage of the patient's entire blood flow through the dialysis machine every 15 minutes, at flow rates of approximately 200–400 ml/min.[3]. This is far higher than the flow rate through the average peripheral vein. Therefore, haemodialysis either requires vascular access via a large bore catheter into a central vein, or an abnormal connection created between a peripheral artery and vein to increase blood flow through that vessel. Central venous access has a high rate of complications, with increased risk of infection, thrombosis and stenosis of the vein amongst them. Initiatives like the National

Kidney Foundation–Dialysis Outcomes Quality Initiative (NKF-DOQI), and later the Fistula First Breakthrough Initiative (FFBI) in North America have been working to increase the number of arteriovenous fistulae created and used, both in the USA and worldwide, in an effort to limit these complications and increase longevity of vascular access in RRT.

Permanent vascular access can be created via two methods: by using either the patient's existing vasculature (autologous), or by placing a vascular graft. In order for it to provide the required flows for adequate haemodialysis, an abnormal connection between the arterial and venous system must be created – a shunt. This then creates a connection between a high and a low-pressure system, allowing more blood to flow via the low-pressure system (the vein or graft), rather than down the artery. This provides sufficient flow for dialysis to take place without accessing the central vasculature.

These shunts can theoretically be placed between any artery and vein in the body. However, as the goal is to provide access for as long as possible with the lowest complication rates, there are certain rules that are followed when an access site is chosen. The access is always placed as distally as possible (i.e. placed in the forearm rather than the upper arm) to preserve proximal sites for future use[4]. The upper limb is chosen rather than the lower limb (lower infection rates, more accessible for use, high incidence of lower extremity venous occlusive disease, higher incidence of arterial steal[4]). As autologous fistulae have better patency rates, they are chosen before grafts[1].

Currently, the gold standard of imaging of existing fistulae is contrast fistulography[5], an invasive testing modality. AVFs found to be dysfunctional are then considered for interventions to be performed at the same time. This modality has significant associated complications, including contrast allergies and puncture site complications, such as false aneurysms. The most commonly used non-invasive modality is the colour-flow or duplex Doppler, which has shown reasonable

accuracy when compared to invasive angiography, and gives structural as well as flow rate information[5]. Flow rates can also be measured by ultrasound measurement of saline dilution via ultrasound probe, a well-documented non-invasive measurement technique[6].

Magnetic resonance angiography (MRA) has also been previously assessed as a useful imaging modality in these fistulae or grafts. It used phase contrast methods that measured flow in two directions of each slice. It has good sensitivity and specificity in comparison to contrast fistulography and doesn't require contrast injection. However, the complexity of flow in these vessels was felt to be a limitation in the accuracy of assessing the fistulae and their complications[7].

However, newer technology has now permitted advances in this imaging technology. The complexity of flow can now be resolved using phase contrast velocity encoding in three dimensions, and spatial encoding in three dimensions. This allows us to track complex blood flow patterns though multiple segments, and track the velocity changes as induced by outside vectors. This data is time-resolved and ECG-gated. It allows for both particle tracking to follow flow patterns, as well as other haemodynamic data to be calculated, such as wall stress and shear stress. It also provides information for computational flow dynamics to build models of vessels.

1.4 Aims and objectives

- Recruitment of study participants.
- Performing MRI scans on each study participant.
- Analysis of MRI data to quantify blood flow.
- Comparison of blood flow between different patient groups and healthy volunteers.

1.5 Methods

Patients will be recruited from the chronic haemodialysis programme at Groote Schuur Hospital renal unit. Healthy volunteers will also be recruited. Should they be willing to participate, they would then receive the patient information sheet and sign an informed consent letter. Their scan will then be scheduled and performed in the next available after-hours slot at the Groote Schuur MRI scanner.

The data from the scan will then be analysed by project team members using MathWorks' MATLAB image processing toolbox. This data will then be converted into numerical values, giving flow velocities at segmental points along the vessel scanned.

Ethical considerations

All study participants will receive a patient information sheet, and sign an informed consent before taking part in the study (see appendices). As such, they will be aware of the aims and objectives of the study, as well as the procedures that will occur during the study. Patients will be fully informed of the procedure for the scan. Participating in this study will not affect their treatment or position in the dialysis programme in any way, either positively or negatively.

Inconvenience to study participants will be limited by provision of transport for participants to and from the scan, as well as some refreshments. They will receive no medications, contrast or invasive procedures. They will receive no monetary reimbursement. All data collected will be stored anonymously in secure servers, and will only be made available to study investigators. Any complaints or issues unable to be addressed by myself or my supervisors will be referred to the Human Research Ethics Committee, and contact details are available in the patient information sheets.

1.6 Work plan and budget

Timeline

Patient recruitment and MRI scanning – November 2013 to February 2014

Data analysis by MRI experts – March 2014 to June 2014

Dissertation preparation – June 2014 to November 2014

Submission – November 2014

Budget

This study is funded by an NRF grant and an associated NRF staff development grant. This allows for payment of cost of scans, transport and study participant refreshments. It also funds presentation of research findings at local conferences.

Provisional costing:

- R2 000: patient transport and refreshments.
- R3 000: cost per MRI of study subject.

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CHAPTER 2
LITERATURE REVIEW

2.1 Introduction

The prevalence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) has increased significantly in recent years. CKD is the ninth leading cause of death in the USA[1]. In 2013, 117 162 new cases of ESRD were reported. Renal replacement therapy (RRT) is expensive. Many of the costs of treatment are associated with the transition onto ESRD therapy, such as catheters, vascular access procedures, failed access and the complications of the above procedures[2]. Eighty percent of the world's population on RRT is in North America, Europe and Japan, which comprise only 15% of the world's total population[3]. In South Africa in 2012, 164 patients per million population were on renal replacement therapy[4]. The mortality rate from ESRD in developing countries is much higher than in the developed world[3]. With the expected increase of hypertension and diabetes in sub-Saharan Africa (130% increase by 2020) and the ever-increasing burden of HIV-associated nephropathy, and therefore downstream increases in CKD and ESRD, all efforts to improve and streamline management of this condition should be made[3].

Long-term RRT by dialysis is dependent upon adequate vascular access. The placement of an arteriovenous fistula or graft has a lower mortality rate compared to dialysis via a central venous catheter, both when done pre-emptively and creating the access early to prevent catheter use, and when converting a patient from a catheter to a vascular access conduit[5].

Another important factor to consider is cost. These patients place an enormous burden on the healthcare system. ESRD and haemodialysis patients consume proportionally far more of the yearly spend than they make up in terms of patient population. In 2010, the treatment of ESRD cost Medicare, the primary funder of treatment of ESRD in the USA, more than $25 billion[6]. In these patients, the most expensive way to deliver dialysis is by catheter. These costs are only equivalent to

vascular access when the access requires multiple procedures to keep it patent. Therefore, making access as efficient as possible is an important goal for both patient care and economic reasons[7].

2.2 Haemodialysis

Haemodialysis is the removal of water and solutes from the patient by using diffusion and convection. Diffusion is the movement of solutes across a semipermeable membrane along a concentration gradient. Clearance of a solute via diffusion is dependent on many factors, including molecular weight, electrical charge, fluid concentration gradient, type of dialysis membrane and blood and dialysis fluid flow rates. Convection refers to the movement of solvent and dissolved solutes across a semipermeable membrane along a hydrostatic pressure gradient. Ultrafiltration is the convective movement of water across a semipermeable membrane[8].

Haemodialysis is the combination of these principles to clear the patient's blood of toxic products of metabolism. The blood is pumped via an extracorporeal circuit, from the patient using the vascular access into the "arterial side" of the circuit. The blood flows through a pressure monitor into the dialysis machine. This machine consists of a dialyser, which is in effect a semipermeable membrane with two different fluid circuits flowing in opposite directions on either side, i.e. blood and dialysis fluid. Machine characteristics differ in terms of membrane type, surface area, permeability characteristics and other components. The blood leaves the dialysis machine via the "venous side" of the circuit. This flows through a pressure monitor and clamp mechanism, and back into the patient via the "venous needle" in the vascular access. The volume of fluid to be removed can be regulated by controlling flow rates of the dialysis fluid[8].

Different types of haemodialysis utilise varying levels of diffusion, convection and ultrafiltration, depending on the requirements of the patient who is receiving dialysis[8]. However, all machines require a minimum flow rate of blood into the

machine of 300–500 ml per minute. In the short term, this can be provided by using indwelling catheters in the central venous system. However, in the case of long-term dialysis, it is mandatory to get permanent vascular access to achieve this high volume blood flow, all the while minimising trauma and complications.

2.3 Vascular access

2.3.1 Central venous access

Central venous access can be achieved by indwelling catheters, either temporary non-tunnelled catheters, or more permanent catheters tunnelled under the skin with a cuff for tissue ingrowth. Temporary catheters are at higher risk of both infection and being dislodged[9]. The catheters insert directly into the central veins (internal jugular, subclavian and femoral), which provide sufficiently high volume flows to perform adequate dialysis. The "arterial side" and the "venous side" of the circuit are provided in a single catheter, either by a split tip or staggered holes in the catheter. These catheters are associated with significant morbidity and should not be regarded as a permanent access solution unless all other access options are exhausted[10].

2.3.2 The arteriovenous fistula

Haemodialysis was initially described in the acute setting in 1943 by Willem Keolf, a Dutch physician. A variety of manoeuvres to gain vascular access were tried, including arterial cutdowns, problematic in a heparinised patient, and direct needling of the arteries and veins. The vessels would then be ligated after a single use, which was not a sustainable practice in the longer term[11]. Attempts to provide multi-use access with rubber tubing left in situ failed because they clotted quickly and caused significant complications[12]. These procedures were also technically difficult and time-consuming to perform. It was only later, in the United States, that the first description of reliable vascular access emerged. In 1960, the report of the first patient to receive chronic haemodialysis was published. Mr. Clyde Shields was dialysed via an arteriovenous shunt made of Teflon, called the "Scribner shunt". Two tapered Teflon cannulae were inserted into the radial artery and adjacent cephalic

vein, and connected externally by a curved Teflon tube. This was later changed to silicon rubber. Remarkably, this patient went on to survive (albeit with a transplant) for a further 11 years. Not surprisingly, these shunts – although a vast improvement on prior techniques – had numerous complications of their own. They fell out, clotted and became infected very easily[11].

At a similar point in time, two physicians had begun to contemplate the same problem of good-quality reusable dialysis access. James E Cimino and Michael J Brescia, physicians in New York, had been working on the problem of access. In 1965, in conjunction with general surgeon Dr. Kenneth C Appell, the eponymous fistula procedure was performed. Published a year later, the classic Brescia-Cimino-Appell fistula involved a side-to-side anastomosis of the radial artery and cephalic vein[13]. This would later be modified to the procedure currently performed today, which involves an end-to-side anastomosis of vein to artery via a 5–6 mm arteriotomy.

The technique described above has been modified for use in other anatomical locations. Most commonly, these involve using the brachial artery as arterial supply, and then the most convenient and best-quality vein for an end vein to side arterial anastomosis.

The vein serves as the access conduit for the dialysis to take place[14]. This arterio-venous fistula can be located on the upper limb in any of three well-described positions, dependent on the patency of the vein and patient anatomy. Potential sites include the “snuffbox” fistula, located at the anatomical snuffbox, or at the wrist, or a looped fistula located more proximally with transposition of the vein to give length for needling[7]. Another commonly used site is the antecubital fossa. Groin fistulae are described but far less common[7]. Fistulae are named according to the artery and vein being used, e.g. radiocephalic, brachiocephalic or brachiobasilic. The vein conduit can either be left in situ or transposed. Transposition implies dissection of the vein from surrounding tissue to either relocate it in the arm or to bring it more

superficially to allow for easier needling during dialysis[15]. The fistula requires a period of maturation, usually about four to six weeks, before it can be used for dialysis. Criteria for maturity can be assessed clinically and radiologically, and the National Kidney Foundation–Dialysis Outcomes Quality Initiative's (NKF-DOQI) "rule of 6" is generally applied. This means that the flow rate should be greater than 600 ml/min., the vein diameter greater than 6 mm and the conduit should be less than 6 mm below the skin surface[16]. However, functional maturity is achieved only when the fistula is first used for successful dialysis. Although the first published series of radiocephalic fistulae had an excellent maturity rate (12 of 14 matured for use), in later years distal fistulae have proven to be more challenging, with a failure to mature rate of up to 66%[17]. There are a number of factors which have been shown to be predictive of failure of maturation in AVF, including age greater than 65, female gender, obesity, peripheral vascular disease, diabetes, cardiovascular disease and wrist location of the fistula. Other important considerations include vein diameter of less than 2 mm and poor vein distensibility[16]. Although the Canadian and American guidelines recommend a radiocephalic fistula as the first procedure of choice, there is strong support for using an upper-arm fistula first in certain high-risk patient subsets, e.g. obese females and diabetics with documented peripheral vascular disease[17].

If the anatomy at the wrist is unfavourable, or patient factors are unsatisfactory, or the patient has had a previous radiocephalic fistula, the next step is to proceed to an upper-arm fistula. The brachiocephalic fistula involves an anastomosis between the brachial artery and cephalic vein. Because of the vein's lateral position, and often minimal dissection, it is the procedure of choice in the antecubital fossa[15]. The second choice is the basilic vein[7]. The downside of this is the need for transposition of the vein, which requires either a more extensive and lengthy procedure, a longer wound or the need for a 2-stage procedure[7].

Clinically significant arterial steal should also be considered when placing the AVF, but it is a relatively uncommon complication. Twenty percent of patients with upper-

arm access will have symptoms of arterial steal (diversion of arterial flow into the fistula, limiting arterial flow to the extremity), but only 4% will have severe enough symptoms to require intervention, which most commonly involves ligation of the fistula[18]. The risk can be minimised by placing the anastomosis as distally as possible.

It is generally accepted that AVFs are superior to the use of vascular grafts[15, 19]. The first NKF-DOQI guidelines published in 1997 encouraged placement of autogenous AVFs[2]. The Fistula First Breakthrough Initiative (FFBI) in the United States in 2003 found that by far the majority (up to 80% in some areas) of prevalent dialysis access was via grafts[5]. It was felt that performing new procedures as AVFs wherever possible would result in a significant cost saving to healthcare in the US[20]. A similar initiative, the CIMINO initiative, was begun in the Netherlands[21]. However, as this programme grew in the US, an unexpected finding appeared: the FFBI showed that there has been a significant increase in the use of AVFs – from 32% in 2003 to 60% in 2012[22]. The increase in use of AVFs has been associated with an increased primary failure rate. a systematic reviewnoted that before 2000, AVFs had a primary failure rate of 10% to 24%. However, in recent years this has increased to up to one third of all fistulae. Forty percent of all AVFs had either failed to mature completely or required at least one intervention to remain patent[23]. Other reviews have shown that, as the proportion of ESRD patients over 65 have increased, there have been higher primary failure rates and poorer primary patency rates[10]. These studies have challenged the recommendation that the forearm fistula always be the first procedure of choice, since it has a higher primary failure rate than an upper-arm procedure[23]. The challenge is to improve the AVF technique to lower primary failure rates and loss of patency while keeping the advantages of an autogenous procedure.

2.3.3 The arteriovenous graft

The “Scribner shunt” is now obsolete shunt technology. In principle, the technique of arteriovenous grafts remains the same, with the use of synthetic graft material

providing a conduit between the artery and vein. The graft can then be needled directly for dialysis.

The choice of graft, both in terms of material as well as location, has evolved over the years since 1960. The materials used have changed from Teflon to Dacron, and more recently to the PTFE (polytetrafluoroethylene) graft used today. Human umbilical vein and bovine graft have also been used and abandoned[12]. Graft location has also changed, with use of the femoral artery and vein now considered a position of last resort after all other access attempts have failed. Novel ideas such as the "button" – a carbon-sealed access plug attached to the vessel with PTFE – have also not shown any longevity[12].

The current practice is an attempt to mimic autologous vein access as far as possible. Implantable grafts are fully internalised and follow a looping course, from distal artery to proximal vein. The key is the choice of material, which should be easy to handle, non-aneurysm-forming, as well as easy to remove if infected or thrombosed. This role is currently filled by the PTFE graft. This material can be modified to be straight, tapered or curved, and diameters range from 4 mm to 8 mm[24]. PTFE can also be layered to include self-sealing elastic layers post needling (GORE® ACUSEAL). Current practice globally is to use ePTFE (expanded polytetrafluoroethylene) grafts[7].

AVGs are positioned according to similar principles as those applied to AVFs. They are preferentially placed distally in the forearm first, and then proceeding more proximally until more atypical sites are considered. They can be placed in a straight or looped configuration, and are attached to the artery distally and the vein proximally. Common sites include the brachial artery to cephalic vein and brachial artery to the more proximal axillary vein. If these fail, more atypical sites include femoro-femoral and axillary-axillary arteriovenous necklace grafts across the chest[7]. Current AVGs are entirely covered by skin and are needled in the same manner as AVFs. Distal placement of the arteriotomy is an attempt to limit the phenomenon of arterial steal[18]. Graft shape can be straight (6–8 mm diameter) or tapered (4 mm–7

mm). However, there is no evidence that tapering of the graft improves patency rates, despite the theory that it would alter the rheology and therefore minimise stenosis and graft thrombosis. It was felt that decreasing shear stress by changing flow geometry would decrease intimal hyperplasia and therefore graft stenosis. Other promising innovation to minimise graft thrombosis and stenosis, such as venous cuffs on the grafts, did not show any benefit in human trials[24].

AVGs provide a valuable alternative option in patients with ESRD who require haemodialysis, but whose anatomy is not amenable to an AVF, because there is no suitable vein to be found, as they all have been used in previous access attempts, or it is felt that the risk of complications was too high[25]. AVGs are often quicker and easier to perform – there is no concern about maturation and they are quickly available for dialysis. However, long-term patency is a problem. A recent systematic review found that when primary failure was excluded, AVFs had a pooled primary patency rate at one year of 60%, and 51% at two years[23]. In comparison, AVGs had primary patency rates at one year of only 40% to 54%, and at two years of 18% to 30%[2]. The secondary patency rates range from 59% to 65% at one year, and 40% to 60% at two years. In direct comparison of the two choices, pooled results found that an AVG was three times more likely to need an intervention and 3.8 times more likely to need a thrombectomy than an AVF[5].

2.4 Failure of dialysis access

Failure of dialysis access can be separated into two categories – primary failure, when the access never matures for cannulation, and secondary failure, when there is loss of patency once it has begun working. Primary failure, or a fistula that is never used for dialysis, is perhaps more accurately referred to as early dialysis suitability failure (if no procedure has been attempted to mature the fistula), or late dialysis suitability failure (if, despite radiological or surgical attempts at intervention, after six months the fistula is still not available for dialysis)[14]. However, in literature the term “primary failure” is taken to mean a fistula that never fulfils criteria for use for dialysis[26].

Primary and secondary patency rates are used to define how long fistulae work for, with and without intervention. Primary or unassisted patency is the length of time a fistula remains functional until the first intervention, which could be endovascular or open. It is often quoted as percentage of conduits that are patent after a period of time, e.g. at six months or one year. Secondary patency is the length of time a fistula remains patent – from initial intervention until access abandonment. It includes any number of procedures to restore patency and, like primary patency, is quoted as a percentage of access conduits that are patent after a specific time period, e.g. one or two years[14].

The causes of primary failure are somewhat ill-defined. There are factors that increase the likelihood of failure, e.g. diabetes, location of fistula, age of the patient[27] and the diameter of the artery and vein being used[16]. However, the pathophysiological process that leads to fistula failure is not clearly understood. In 2008, some early research on primary failure showed that neointimal hyperplasia was not just a cause of later stenosis of the access, but could also be demonstrated in juxta-anastomotic stenosis of primarily failed access[28]. Although the precise mechanism for development of the stenoses is not understood, there are techniques available to treat them. Balloon angioplasty has been shown to be effective, with a 98% success rate in one study, which reduced stenosis to less than 20% of total conduit size[19].

Another cause of primary fistula failure is the presence of accessory veins. The cephalic vein can often have more than one draining accessory vein. This is a normal anatomical variant, but can cause problems with regard to fistula maturation[19]. The accessory vein decreases the flow in the fistula vein, and thus diminishes chances of maturation because of the decreased pressure and flow. Ligation of the accessory vein is a simple procedure that is very effective at salvaging a non-maturing fistula, with up to a 100% success rate[27]. The secondary patency of these fistulae, once matured, is similar to that of fistulae that achieved maturation without intervention.

The procedures required to effect maturation have a low complication rate, and so should be attempted if at all possible[27].

In an attempt to move away from costly surgical procedures, there have been attempts to treat primary fistula failure medically. For example, in primary fistula failure due to thrombosis, two anticoagulants have been tried to improve primary failure rates. Unfortunately, although there was a reduction in the number of thrombosed fistulae, there was no effect on the number of fistulae which could be used for dialysis, i.e. primary functional patency[29].

Late vascular access failure is generally the result of venous stenosis in both grafts and fistulae[30]. In AVGs, the stenosis is usually at the graft-vein anastomosis. In AVFs, it is most commonly juxta-anastomotic[31], i.e. at the first part of the vein to experience arterial flows and pressures. These stenoses form on the basis of neointimal hyperplasia, which involves migration of smooth muscle cells and myofibroblasts, and laying down of increased extracellular matrix[31]. Precisely how the hyperplasia is initiated remains unclear, but fluid dynamics impact on the development and worsening of intimal hyperplasia[24]. Whether the stenosis was present prior to fistula creation, and only becomes clinically significant later on, is difficult to determine, even if preoperative imaging is performed. This is due to the change in flow volume and haemodynamics in that vessel. However, it is well established that venous stenosis must be treated and monitored to prevent thrombosis and loss of access[32].

The benefits of surveillance are less well defined. The Society of Vascular Surgery's clinical guidelines support the use of surveillance of vascular access[26]. Should the surveillance show stenosis of more than 50%, DOQI guidelines indicate that balloon angioplasty should be performed in order to reduce the stenosis to less than 30% of the lumen[15]. Failure to treat these stenoses, whether venous, arterial or juxta-anastomotic, will result in fistula thrombosis, and this is far more difficult to treat.

It is unclear whether the treatment of a thrombosed fistula is better with closed thrombolysis (pharmacological and/or mechanical[33]) or with open thrombectomy. It is important that any stenoses found are treated as well. However, because of the high secondary patency rates, salvage of a thrombosed fistula is worthwhile[32]. There has been a substantive growth in novel therapies to minimise and treat access thrombosis, such as drug-eluting stents, grafts, and wraps, and endovascular radiation. These are all in the laboratory phase and have not been tried in clinical practice[31, 34].

2.5 Imaging of vascular access

2.5.1 Duplex ultrasound

Duplex ultrasound is widely used to image AV access. It is non-invasive and includes imaging of the vessel as well as information about flow within the fistula. It is a combination of pulsed Doppler spectral analysis, B-mode ultrasound and colour Doppler imaging[35]. Duplex ultrasound for diagnostic purposes in dialysis access was first validated in the late 1980s, when it had been available commercially for only a few years. It was recognised that an imaging modality that could non-invasively assess both anatomical and flow information would be valuable in the setting of dialysis access. The technique used included mapping of the entire access using linear high-frequency probes for b-mode or colour Doppler vessel imaging and flow rate measurement, and pulsed wave Doppler velocity spectra measurement for stenosis classification (i.e. more or less than 50%)[36]. When compared to angiography, which is the gold standard, it was found that duplex ultrasound had an accuracy of 96% when diagnosing efferent vein stenoses (sensitivity 95%, specificity 97%). The accuracy of diagnosing anastomotic stenoses in radiocephalic fistulae was less at 81% (sensitivity 79%, specificity 84%)[37]. Subsequent studies found a lower level of accuracy, with approximately 80% sensitivity and specificity[36], which was still accurate enough to make duplex ultrasound the first imaging investigation of choice, as well as a useful adjuvant to other imaging[38]. It is currently recommended in the NKF-DOQI initiative that duplex ultrasound be used in the surveillance of dialysis access. However, the evidence for this recommendation is weak[26].

Nonetheless, surveillance with a combination of duplex ultrasound and physical examination is recommended according to the algorithm in the DOQI initiative[36]. The most important caveat to the use of duplex ultrasound is that its results are operator dependent. Most errors result from incorrect technique by the technologist, and a small change in technique can have a large change in results[35]. For this reason, it is encouraged to only use an accredited vascular laboratory for dialysis access surveillance. Duplex ultrasound of dialysis access is noted to be particularly difficult, due to vessel tortuosity and high-peak systolic velocities causing increased flow and artefact, especially at the arterial anastomosis[36]. Another limitation of duplex ultrasound diagnosis is that the access may be failing due to central vein stenosis, which duplex ultrasound does not easily detect. This should be borne in mind when reviewing results.

2.5.2 Contrast fistulography

Contrast fistulography is currently considered the gold standard of fistula imaging[36]. The technique involves cannulation of the venous outflow tract and contrast injection. If this does not provide adequate arterial imaging, a cuff can be used to obstruct venous outflow or a guide wire and catheter advanced down into the artery to inject the contrast. The images should be obtained in multiple planes to limit obscuring tortuous vessels and aneurysms. These are then reviewed after digital subtraction. The major advantage of digital subtraction angiography (DSA) over non-invasive imaging techniques is that it allows for simultaneous intervention. This limits the number of procedures, and therefore the cost of failing access salvage. It also allows for imaging of both the entire tract as well as the full venous outflow, permitting diagnosis of central venous stenosis. It has been suggested that when performing (or planning) percutaneous intervention for failing fistulae, full imaging of the outflow tract should always be performed, as central stenosis is too often missed by duplex ultrasound[39].

The limitations to fistulography are numerous. It is invasive and has complications that include access rupture and access thrombosis. It requires the use of ionising radiation, which must be borne in mind, as these patients often require multiple

procedures over the years to maintain access patency (Dixon et al. 2009). It also requires the use of intravenous contrast, which would be deleterious to whatever residual renal function there is. For these reasons, it is seldom used in isolation, and should be considered an intervention modality rather than purely an imaging modality[39].

2.5.3 CT fistulography

CT angiography, especially since the advent of multislice helical CT scanners, provides very good quality images of arteries[40]. The faster acquisition times and increased number of images per unit area help to provide detailed images of the vessels of interest. It has not been used widely in terms of dialysis imaging. However, in one small study it showed equal sensitivity and specificity to DSA when diagnosing stenoses[41]. Unfortunately, CT fistulography combines the disadvantages of MRA and DSA, in that it requires venepuncture (against the principles of access site conservation of the DOQI) and the use of intravenous contrast. Furthermore, it uses ionising radiation. However, unlike DSA, it does not provide the option to perform intervention, which is the benefit that outweighs the risks of intravenous contrast and radiation.

2.5.4 MR angiography

Magnetic resonance angiography (MRA) is another non-invasive imaging technique that has not been studied extensively, but could be used as an adjuvant imaging technique. Small studies have shown that it is sufficiently accurate when compared to contrast fistulography[42-44]. There have also been attempts to use 2D CINE PC in measuring flow in dialysis access, which, although limited by the early stages of MRI software, showed good reproducibility and that such measurements were feasible[45, 46].

Like CTA and duplex, it is non-invasive, but unlike duplex, it is not operator dependent. Unlike CT, it does not require the use of ionising radiation. However, some techniques require intravenous gadolinium contrast, and this has led to the

development of nephrogenic systemic fibrosis, which is a rare complication. This can present with limb oedema, muscle weakness and fibrosis, including the diaphragm and oesophagus, and skin lesions such as cutaneous papules and plaques. The only consistent link is that it occurs in patients with poor renal function and is strongly associated with gadolinium administration[47]. This must be taken into account when considering contrasted MRA in patients with dialysis access, who by definition have poor renal function. MRA is costly, both in terms of price and the time it takes to perform the examination[42]. It is described for second-line imaging after duplex ultrasound, or if there was a non-diagnostic segment on DSA[44].

2.5.5 4D flow-sensitive MRI

Magnetic resonance imaging (MRI) generates images through the application of three magnetic fields: the main external field, magnetic field gradients and an applied oscillating field. The external field aligns all the protons of the image subject within its field (protons are hydrogen atoms and, because of the high proportion of hydrogen in human cells, it is their signal that generates an MRI image). The applied gradients turn the external field on and off in a linear fashion, changing the resonance of the protons. The placing of a coil provides the final oscillating or radiofrequency field, which forces the protons to resonate and produce a signal. A mathematical algorithm called the Fourier transform is then used to convert the signal into an image[48].

The application of gradients and fields form a pulse sequence that is specific to the type of tissue that is being imaged. These pulse sequences are designed to provide more or less weighting to different types of relaxation (the loss of the longitudinal and transverse magnetisation provided by the magnetic fields), i.e. T1 and T2. This permits very fine differentiation of tissues, and provides the soft tissue detail that MRI is so well known for. Imaging of blood puts more emphasis on the T2 signal[48].

4D MRI captures images using phase contrast technology. A bipolar gradient is applied between the excitation pulse and the readout. Two images are collected and compared. The moving particles acquire a different phase along the applied gradient,

and can therefore be differentiated from the static particles. The static particles (and image of static tissues) are subtracted, and the final image is generated. The gradients are applied according to expected velocities of moving particles (in our case, blood). The change in phase also allows for the velocity of these moving particles to be calculated. These images are acquired in three directions, and cover the entire volume of the imaged area. The addition of ECG gating means that these images are said to be collected in "four dimensions", three spatial dimensions and time[49].

This was initially used in larger vessels such as the aorta, and subsequently in progressively smaller vessels as image acquisition and data processing technology improved. When 3D phase contrast became available, it permitted analysis of more complex flows[49], a hallmark of dialysis access on duplex ultrasound[36].

One of the advantages over previous 2D CINE PC MRI is that because it gathers the same velocity data over the whole 3D volume, analysis of a specific area can be performed at any point throughout the volume without risk of plane misalignment, and therefore incorrect results. It has been found to be both accurate and reliable, even though pulse sequences and data analysis tools are constantly being updated[50]. For example, 4D MRI, when used to image stenosed renal arteries, provided data about haemodynamically significant stenoses that correlated with invasive pressure measurements in animal studies[51]. It not only provided imaging from the scans themselves, but the data could also be used to cross-validate and enhance computational flow dynamic models, which are proving to be useful in the field of vascular flow dynamics[52]. Limitations in this technology include the length of time taken to scan the required volume, but this is improving[53].

2.6 Computational flow modelling

The science of computational flow modelling is based on the application of the Navier-Stokes equations, which have changed greatly since first inception. They are a set of equations designed to predict the actions of a single-phase fluid under certain

predetermined conditions[54]. These equations were initially used in settings such as aircraft design (air flow), but as access to high-power computing has improved, they are being applied more widely across many fields, including that of haemodynamics. This means that, by using these equations, one can predict the path, speeds and shear stresses applied by a fluid in a predefined area, such as a dialysis fistula or graft.

In order to calculate predicted flows, a set of boundary conditions must be applied. These include the type of fluid and the conditions at the physical edges of the area to be modelled – the flow rate, volume of the area and pressures.. The more accurate the boundary conditions, the better the predictive accuracy of the fluid dynamics. These boundary conditions are determined from available information, either estimated or measured[55].

Previous studies have attempted to determine if changing specific anastomotic angles will change haemodynamic conditions at anastomotic sites, and thereby decrease fistula failure[55]. This information was calculated using boundary conditions which were either estimated or measured using a variety of imaging techniques such as duplex Doppler and digital subtraction angiography[56, 57]. These studies provided promising results,suggesting that an alteration of anastomotic angle could change the wall shear stress or oscillatory shear stress index, which may decrease intimal hyperplasia[55]. However, it must be remembered that flows in a dialysis access fistula or graft are far more complex than flows in a vascular arterial bypass graft (the blood flow rate alone is 5–10 times higher), and therefore the effects of changes in technique are far harder to predict[58]. Previous studies have shown a correlation of results from CFD modelling and imaging using duplex Doppler[59].

4D MRI could therefore fulfil two roles: it could provide accurate boundary conditions for the computational modelling, which would allow high-quality model building and data generation, and also, by using particle tracking image generation, flow rate measurement and wall shear strength calculation, it could provide validation for those calculations. However, before this can take place, imaging protocols must first be designed to see if it can be used in these difficult vessels.

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CHAPTER 3
Journal ready manuscript

3.1 Introduction

The incidence of end-stage renal disease (ESRD) in sub-Saharan Africa is increasing. In 1994, there were 70 people per million population (pmp) receiving renal replacement therapy. In 2012, there were 164 pmp[1]. The treatment of ESRD, while including managing causative diseases and complications of the ESRD, requires renal replacement therapy (RRT). The ideal way to do this is via a renal transplant[2]. The alternative option for replacement therapy is dialysis, which is able to fulfil some functions of the failed kidney. Dialysis can be provided by two methods: either by using machines to perform the filtration function of the kidney on blood circulated through them (haemodialysis), or to use the patient's peritoneal membrane to act as a filter to remove dialysates from the blood (peritoneal dialysis). If peritoneal dialysis is not an option, ESRD patients are placed on a haemodialysis programme.

In South Africa, the current renal transplant rate is 4.7 pmp, far lower than the 164 pmp receiving RRT[3]. Even in the USA, the median time to renal transplant is 1.71 years[4]. Efforts are made to minimise time on haemodialysis programmes and improve access to transplants, but the current reality is that the average patient can spend (depending on various factors) months to several years on haemodialysis.

Haemodialysis requires high flow access to the patient's circulating blood volume[5]. The ideal access should be safe, cause minimal complications, have a long usable period, be usable early, be comfortable and cosmetically acceptable for the patient, economical, and not require repeated interventional procedures for the patient[6]. Currently, access is either via central large bore vascular catheter, or preferably arteriovenous fistula (AVF) or arteriovenous graft (AVG)[7]. These are generally peripheral procedures, placed most often in the upper limb, and provide a sufficiently

high blood flow rate in a smaller peripheral vessel to allow adequate haemodialysis to take place. Both of these options are far from perfect. The biggest complication of peripheral access is failure, either of maturation or thrombosis[8, 9]. As each patient has only limited sites suitable for AVF or AVG creation (due to variations in patient anatomy and complications from previous lines and procedures), every attempt should be made to make each access AVF or AVG the last one for that patient.

"*Every failed vascular access is a nail in the coffin of an ESRD patient.*"
– Prof D Kahn

In order to optimise access performance, information about the structure of the AVF or AVG as well as haemodynamics of the flow through the access is required. A new type of magnetic resonance imaging (MRI), 4D flow-sensitive MRI, makes use of existing MRI machines and new analysis software to generate data – not only about structure, but also haemodynamics[10]. If the imaging provides enough detail in terms of flow rates and directions, it will be used to help build models of dialysis access. The models can then be used to see if alterations in technique or materials would improve patency rates, decrease maturation times and decrease complications. However, 4D MRI has never been used on such distal vessels, or on such complex flows before, and has never been used to provide data for modelling on such vessels. The following study attempts to pilot this technique in such vessels to see if such a project would be feasible.

3.2 Methods

The study was approved by the UCT Human Research Ethics Committee (HREC REF719/2013). The patient information sheet and informed letter of consent are attached in the appendices. A total of 14 participants were included in the study. The demographic data, including the age, gender and cause of ESRD, as well as type and age of access were recorded. Racial demographics were not recorded.

The control group consisted of six young, healthy volunteers who were recruited from the general public. They had no history of significant vascular or medical conditions, and no attempt was made to control for relative hyperaemia after

exercise, fluid consumption or other variables. There were eight patients with ESRD on dialysis included in the study. Scans on dialysis patients were performed at least six hours after dialysis in an attempt to control for the wide variation in fluid balances in these patients. Access patients were recruited from the chronic haemodialysis programme at Groote Schuur Hospital's renal unit.

All vascular access in these patients were created as surgical procedures by the Groote Schuur transplant unit. The operations were performed under either local or general anaesthesia. The upper limbs were examined and a suitable vein identified by clinical examination and ultrasound. If there was no suitable vein for an AVF, the decision was taken to perform an AVG. For upper-arm AVF, the skin incision was made in the antecubital fossa, and the vein gently dissected free of surrounding tissues to gain as much length as possible. Any visible accessory branches are ligated. The brachial artery was then dissected and controlled with vessel loops. The vein was ligated and divided as distally as possible, and anastomosed to the brachial artery using 7/0 nonabsorbable sutures.

The insertion of the AVG involved the anastomosis of a 6 mm PTFE graft between the brachial artery in the antecubital fossa distally, and the axillary vein in the distal axilla proximally, via a tunnel subcutaneously on the lateral aspect of the upper arm. The anastomoses were made with 6/0 nonabsorbable sutures.

All study subjects were informed as to the aims and methods of the study. Informed consent was taken and included, but was not limited to full consent about the MRI scanner and the presence or absence of contraindications to a MRI scan. MRI scans were performed at Groote Schuur Hospital after hours in the Siemens Magnetom Symphony 1.5T MRI Scanner. The MRI scans were performed between March 2013 and November 2014. A standard 30 cm body coil was used, and the area scanned was dictated by the position of the coil. This was placed over the upper-arm dialysis access by the assisting MRI radiographer. The area scanned was limited by the size of the coil. All scans were performed with simultaneous ECG recording, providing the data for cardiac gating.

The MRI acquisition settings were optimised throughout the study. They were initially derived from the 3D MRI velocity mapping package developed by Markl et al.

The scans were collected and stored anonymously. They were analysed with the following points of interest selected: the brachial artery proximal to the arteriovenous anastomosis, the anastomosis itself, and the outflow in the fistula.

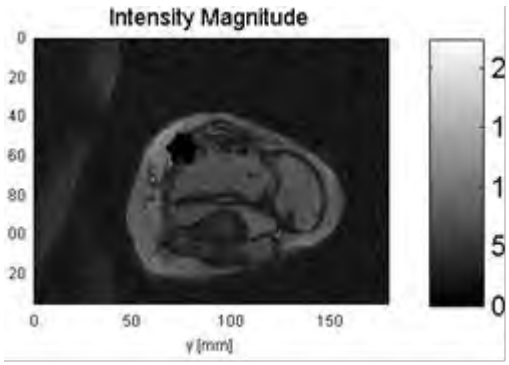
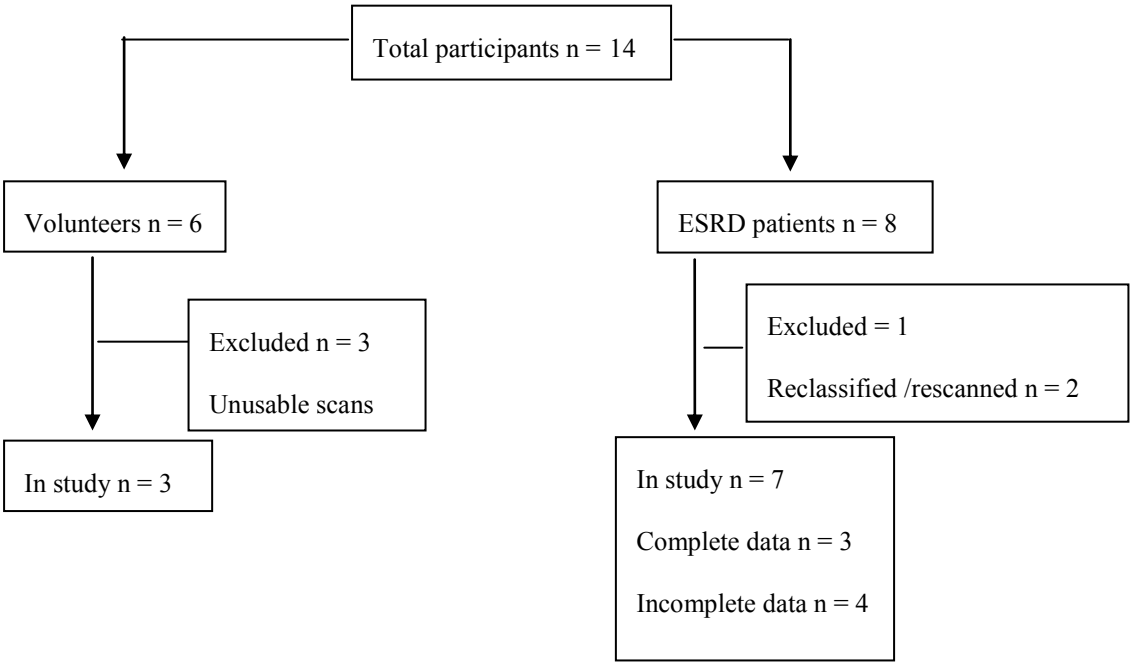


Figure 1: MRI slice from AVF 3 – determined point of interest is the pitch black cross-sectional area over the vessel.

The images were pre-processed and the data analysis undertaken as part of other related postgraduate research projects. Software used for pre-processing and analysis included MathWorks' MATLAB image processing toolbox and previously developed pre-processing and visualisation GUI and code[11], Super Tool v026, as well as VeloMap Tool[12] and flow Tool[13]. The images generated numerical values, giving flow velocities at the determined areas of interest along the vessel. 2D scans generated axial velocities at designated areas of interest on the MRI slices, and the data generated from the 3D time-resolved scans (or 4D) was then processed for particle tracking. The variables used in this study were velocities and flow rates, measured in centimetres per second (cm/sec) and millilitres per minute (ml/min.) respectively.

The 3D post-processing programme generated data in three axes viz x, y and z, with z being the axis of "forward" or axial flow. Each point of interest was divided up into "voxels", which are areas of the scan measuring 1.56 x 1.56 x 2 mm, and velocities were calculated within these areas. Positive numbers indicated flow in the expected direction (i.e away from or returning to the heart). The z-axis data was used to calculate the mean flow velocity and volume.

Unfortunately, some scans did not provide usable data. The results from volunteers one and two were not included as they were early attempts at scan protocols, and the settings did not provide usable data. The scans from volunteer five were localised on the wrong vessels, and therefore the results were not relevant to this study. AVF 1 had incorrect placement of the scan field, and therefore these results were also not usable. Those scans were repeated and the results were presented under AVF 4. AVF 2 was initially misclassified, and the results were given under AVG 3. AVG 3 only had brachial artery and graft midpoint data due to the initial misclassification, which resulted in errors in placement of the MRI arm coil. Similarly, results for AVG 1 were not available due to the software not being able to unwrap data correctly. Some of the results from AVF 3 and 7 and AVG 2 and 3 did not unwrap correctly using the software, and were therefore not available.



Duplex Doppler ultrasound scans were performed on two patients to confirm that the velocities generated by the software were in the correct range. The duplex Doppler ultrasound scans were performed just prior to MRI scanning. The first duplex on AVG 2 was performed by a dedicated vascular ultrasonographer on the Toshiba Aplio 400 machine, whereas the second ultrasound was performed on a portable cardiovascular ultrasound system (Vivid I, GE Healthcare) by a different trained team member.

3.3 Results

Patient data

There were six healthy volunteers in the study, consisting of four males and two female, with an age range of 23 to 29 years. The ten ESRD patients included six females and four males, with an age range of 22 to 55 years. The original causes of ESRD included hypertensive nephropathy, chronic glomerulonephritis, and nephrotic syndrome. The age of the dialysis access varied from 12 to 15 months old. The ESRD patients included five with an AVF and two with a PTFE AVG.

Haemodynamics

Volunteers

The flow velocities in the brachial artery in the healthy volunteers ranged from 5.8 cm/sec to 6.2 cm/sec. The flow rates in the brachial arteries of the volunteers ranged from 25.8 ml/min. to 52.1 ml/min.

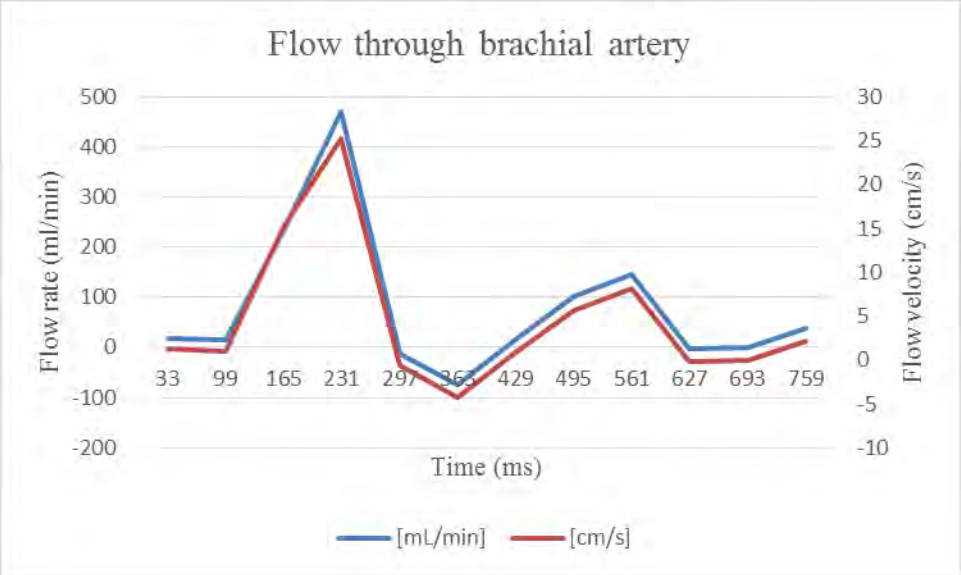


Figure 1: Flow rate and flow velocity through the brachial artery in healthy volunteer five.

Figure 1 is a representation of the flow through the defined point of interest in the brachial artery of volunteer five. The time in milliseconds on the x axis is provided by the ECG gating, and the changes in flow and velocity correlate with the cardiac cycle. The flow through the point of interest very closely resembles the cardiac cycle, with a large increase of flow rate and velocity in systole, and a much smaller diastolic peak later in the cycle.

ESRD patients

The average flow rates and velocity generated using MRI data in the ERSF patients and healthy volunteers in the various regions of interest are shown in Tables 1 and 2 respectively.

Flow rate

	Arteriovenous fistula (AVF)					**Arteriovenous graft (AVG)**		**Volunteer**		
	03	**04**	**05**	**06**	**07**	**02**	**03**	**03**	**04**	**06**
Brachial artery	?*	2477.0	2186.7	1729.6	2162.5	1431.3	1528.7	52.1	46.3	25.8
Anastomosis **Arterial side** **Venous side**	957.0	1857.3	3507.6	?*	– 1158.6 2827.8	– 660.0 1681.0	– ?* ?*	–	–	–
Fistula/graft	?*	1967	4398.1	2809.2	787.5	–	698.3	–	–	–
Cephalic vein	–	–	–	–	–	–	–	10.8	6.9	27.9

Table 1: Flow rates (ml/min.) in ESRD patients with AVF or AVG, and healthy volunteers.

?* = indicates no result available, either due to poor data unwrapping or incorrect coil placement.

Flow velocity

	Arteriovenous fistula (AVF)					**Arteriovenous graft (AVG)**		**Volunteer**		
	03	**04**	**05**	**06**	**07**	**02**	**03**	**03**	**04**	**06**
Brachial artery	?*	85.5	93.2	80.7	95.0	60.1	62.4	5.8	8.5	6.2
Anastomosis **Arterial side** **Venous side**	34.3	68.3	22.9	?*	– 42.0 67.1	– 63.3 85.0	– ?* ?*	–	–	–
Fistula/graft	?*	10.4	24.7	69.6	15.6	?*	6.8	–	–	–
Cephalic vein	–	–	–	–	–	–	–	1.4	4.3	14.2

Table 2: Flow velocity (cm/sec) in ESRD patients with an AVF or AVG, and healthy volunteers.

?* = indicates no result available, either due to poor data unwrapping or incorrect coil placement.

The flow rates in the brachial arteries of AVF patients ranged from 1 729 ml/min. to 2 477 ml/min. These were much higher than in the healthy volunteers (25.8 ml/min. to 52.1 ml/min.). The flow rates ranged from 957 ml/min. to 3 507.6 ml/min. through the arteriovenous anastomosis. Due to the large diameters, these fistulae were still able to provide high volume flow, which ranged from 787 ml/min. to 4 398.1 ml/min. However, the flow velocities in the fistula itself were far lower than in the brachial artery, and ranged from 10.4 cm/sec to 69.6 cm/sec. The velocity through the anastomosis ranged from 15.7 cm/sec to 68.3 cm/sec.

There was an increased mean flow rate in the brachial arteries of the vascular access patients (1 919 $\pm$ 380 ml/min.) compared to the healthy volunteers (41 $\pm$ 11 ml/min.). There was a similar increased mean flow velocity in the brachial artery of the vascular access patients (79 $\pm$ 14 cm/sec) compared to the healthy volunteers (6.83 $\pm$ 1.18 cm/sec).

The small sample size does not permit true comparison of flow volumes and velocities between grafts and fistulae. It is worth noting that, despite their slower velocities, the fistulae still managed to carry more than sufficient volume for adequate dialysis (>500 ml/min.).

These numbers were averages over multiple cardiac cycles and therefore cannot represent the complexity of the haemodynamics in these vessels. However, a closer look at the source data that generates the averages mentioned above illustrates the complexity of the haemodynamics. Table 3 below shows the maximum and minimum velocities collected over 28 time points in the cardiac cycle in the “z axis” or forward flow. The wide variations in numbers show how turbulent the flows are, both in terms of the difference between each voxel at the area of interest, as well as the difference between maximum and minimum flows during the cardiac cycle.

Flow velocities in AVF 7 arterial side of the anastomosis, voxel by voxel

Vz	Vz	Vz	Vz
Max	**Min**	**mean**	**Stddev**
74.16992	-90.234	23.7793	38.16601
78.44238	-64.770	34.68863	31.0278
82.88574	-33.837	35.06611	30.16268
82.03125	-43.579	36.66804	30.91183
82.54395	-41.015	38.00143	30.57033
89.72168	-39.648	39.73483	30.86187
85.62012	-51.782	39.85502	30.15612
81.00586	-55.371	39.24467	30.45496
101.001	-72.631	44.13687	41.71875
122.5342	-130.22	53.41046	55.61971
142.0166	-175.17	53.82174	73.73747
161.8408	-164.06	53.20951	70.60018
125.6104	-218.75	50.15587	66.6831
134.1553	-128.85	46.75293	59.88894
129.0283	-190.21	45.78576	58.69188
120.8252	-139.11	46.8919	54.46475
108.3496	-161.32	41.97529	48.72214
102.5391	-122.53	40.97055	43.9936
88.35449	-47.680	37.58451	34.07297
83.05664	-61.865	37.4831	35.43361
92.96875	-152.44	39.23528	44.07499
96.72852	-110.05	40.8297	45.66434
101.001	-112.62	43.94531	47.73145
98.4375	-112.96	44.08428	44.35089
102.5391	-76.049	43.50586	43.17241
105.4443	-94.165	42.86546	42.34809
125.4395	-43.579	44.27209	37.83868
90.40527	-116.21	40.69073	38.71687

Table 3: Z axis (Forward-flow) velocities through each voxel in the region of interest of fistula seven – the arterial side of the arteriovenous anastomosis over one cardiac cycle.

This was a pilot study, designed to develop an entirely novel method of scanning dialysis access. As the pilot proceeded, scan settings and localisation became more accurate, which resulted in the generation of more data from each scan.

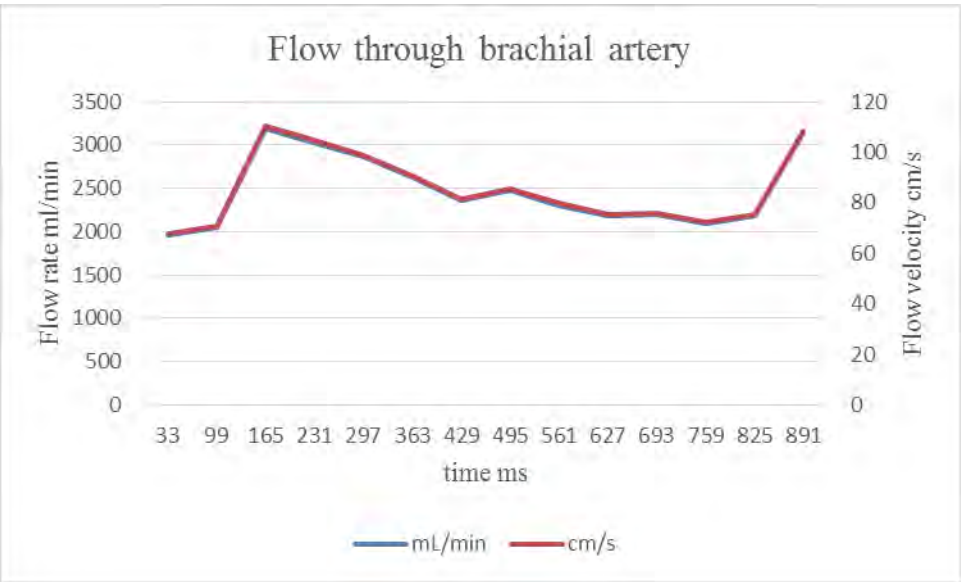


Figure 2: Flow rate and flow velocity through the brachial artery of AVF 4.

The above graph (Figure 2) shows the limited number of data points in an early scan in comparison to Figure 3 below. The final scan, AVF 7, generated more areas of interest, with more recordable flow rates. It also allowed us to look at flow rates across smaller areas in the areas of interest. A single averaged number or table cannot convey all the information. Figures 3–6 display flow rate and flow velocity versus time over a single cardiac cycle of AVF 7.

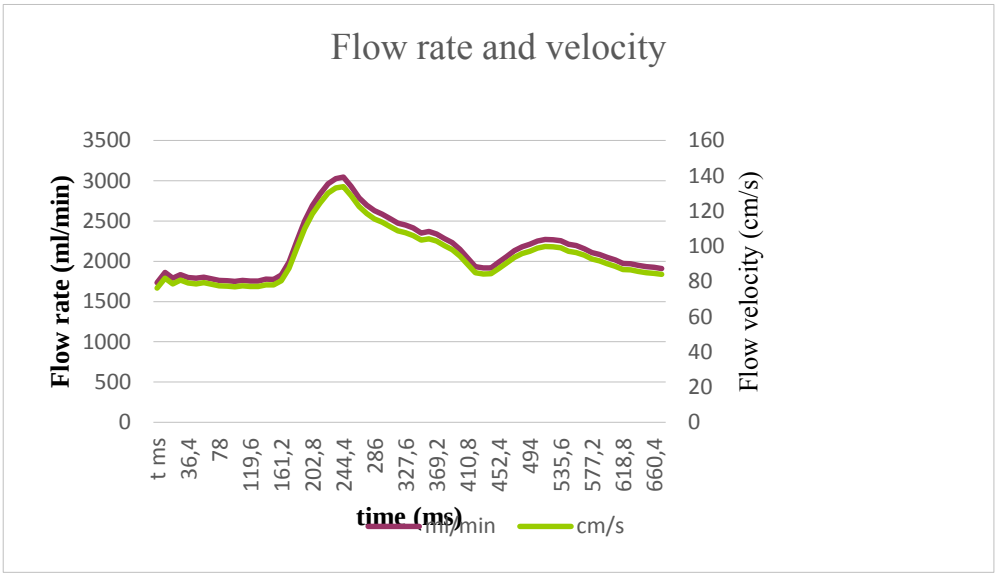


Figure 3: Flow rate and flow velocity in the brachial artery of AVF 7.

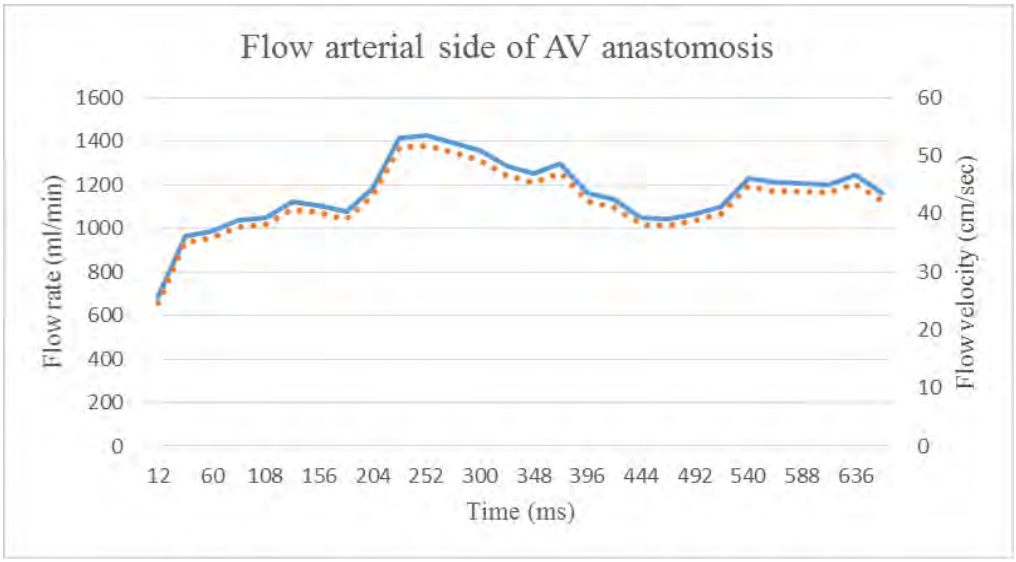


Figure 4: Flow rate and flow velocity on the arterial side of the arteriovenous anastomosis of AVF 7.

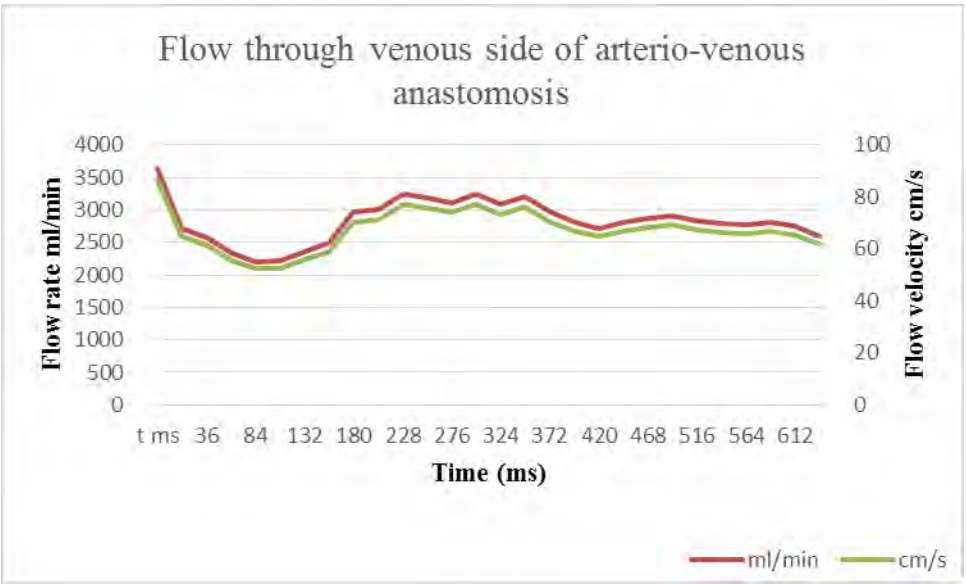


Figure 5: Flow rate and flow velocity on the venous side of the arteriovenous anastomosis of AVF 7.

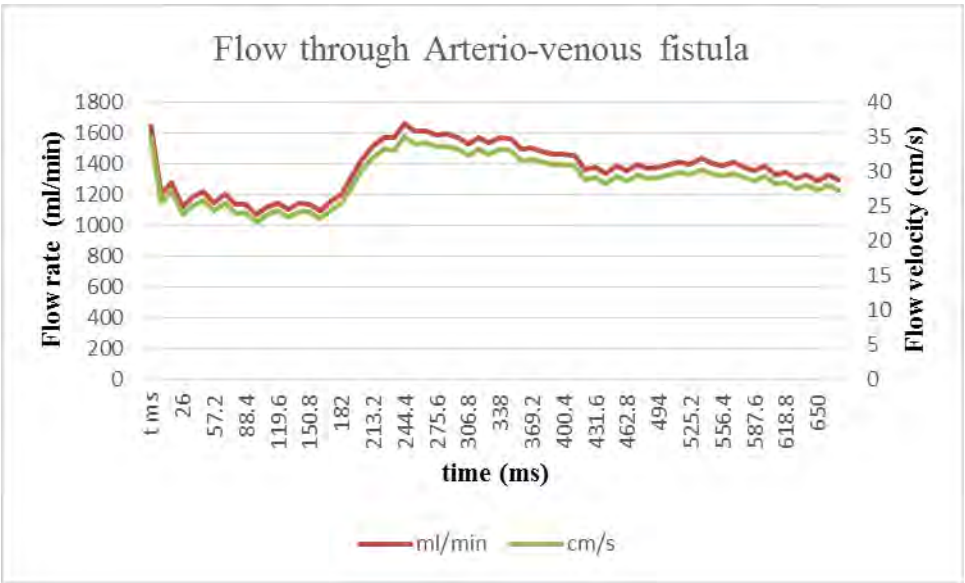
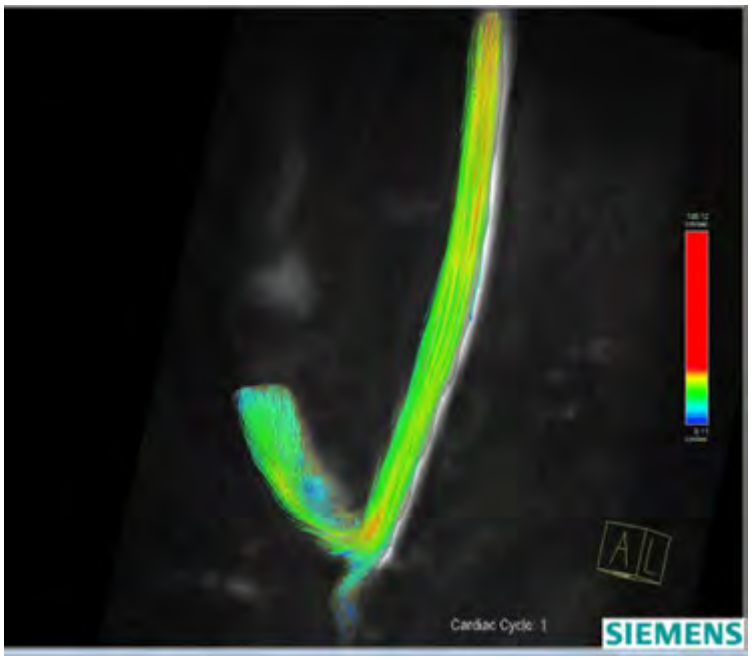


Figure 6: Flow rate and flow velocity of the fistula of AVF 7.

The graphs in Figures 2–6 should be compared, firstly to each other, and then to the graph displaying flow in the healthy volunteer's brachial artery (Figure 1). The marked differences in shape and variability of the graphs indicate the different haemodynamics experienced by each area of the access. It is also worth noting how different the flows in the different sides of the arteriovenous anastomosis are, despite it being such a small area.

One of the advantages of the 4D flow-sensitive MRI is that it allows "particle tracking", which is a visual and colour-aided demonstration of flow throughout a chosen vessel. Data was collected and encoded in three axes as mentioned above, as well as time (using the ECG gating). The scan sequences and software allowed this data to then be processed into a visual representation, and the flows in each voxel of the starting scan tracked throughout the scan area in the form of "streamlining". Colour is then added to this image to allow easy understanding of both flow direction and velocity through the entire scanned vessel[14]. This could allow us to identify areas of interest to focus on to maximise intervention.



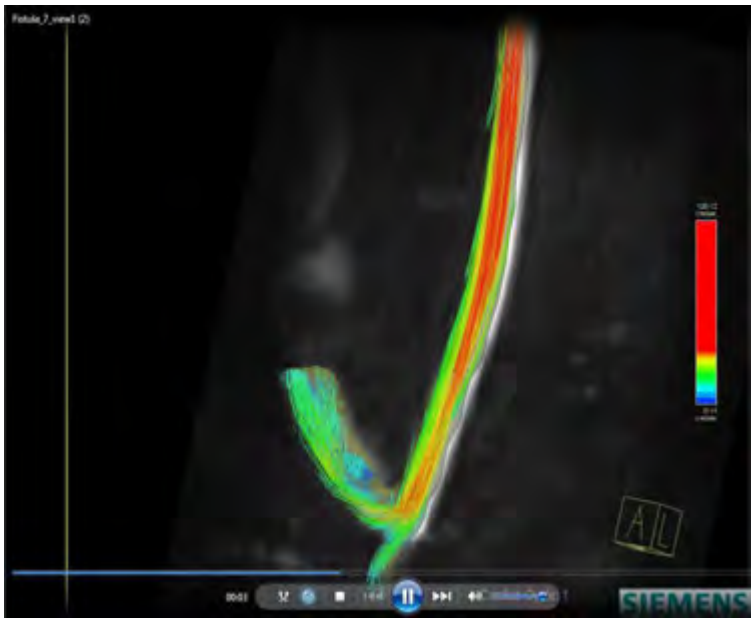


Figure 7: Example of particle tracking still image from AVF 7 (top); example of particle tracking still image showing increased turbulence at arteriovenous anastomosis (bottom).

AVF 7's adequate scan data permitted use of images to perform particle tracking. Coloured still image renderings of flow from the video at points of interest demonstrate the increased turbulence and flow voids shown in the fistula itself in comparison to the brachial artery. The turbulence of the flow through these vessels is marked (Figure 7).

Arteriovenous grafts

Points of interest for velocity and flow calculations in AV grafts were the brachial artery proximal to the graft, the artery-graft anastomosis, mid-graft at the same level as the brachial artery point of interest, and the graft-venous anastomosis. AV grafts were particularly challenging to scan, as the areas of interest were at either end of the graft, and difficult to cover with the single MRI coil for the area. As the prosthetic graft material cannot dilate (and thus the conduit is narrower than the majority of mature fistulae), velocities were expected to be higher to provide similar to the AV fistula.

Brachial artery inflow velocity to the graft ranged from 60.1 cm/sec to 62.4 cm/sec, similar to AVF inflow.

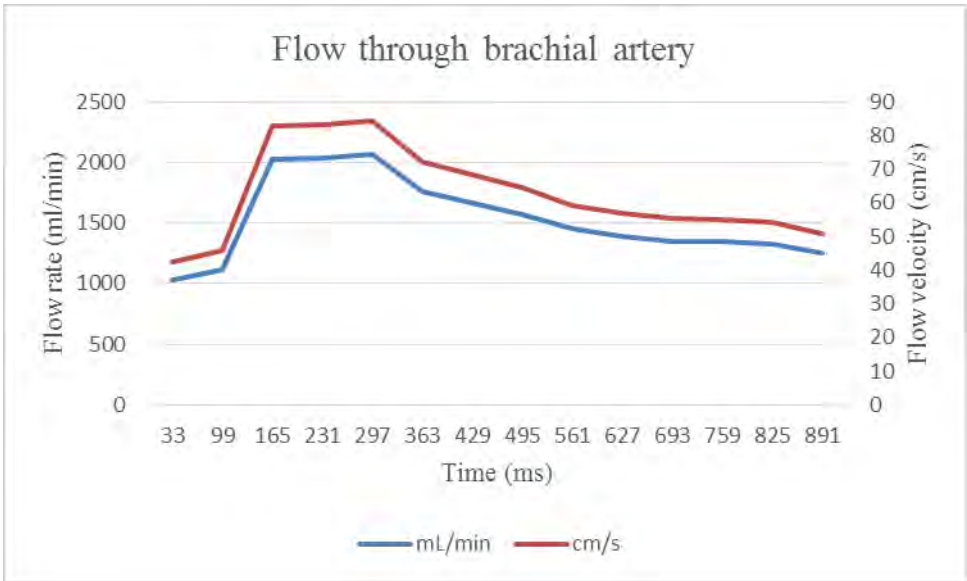


Figure 8: Flow rate and flow velocity of AVG 3 brachial artery inflow.

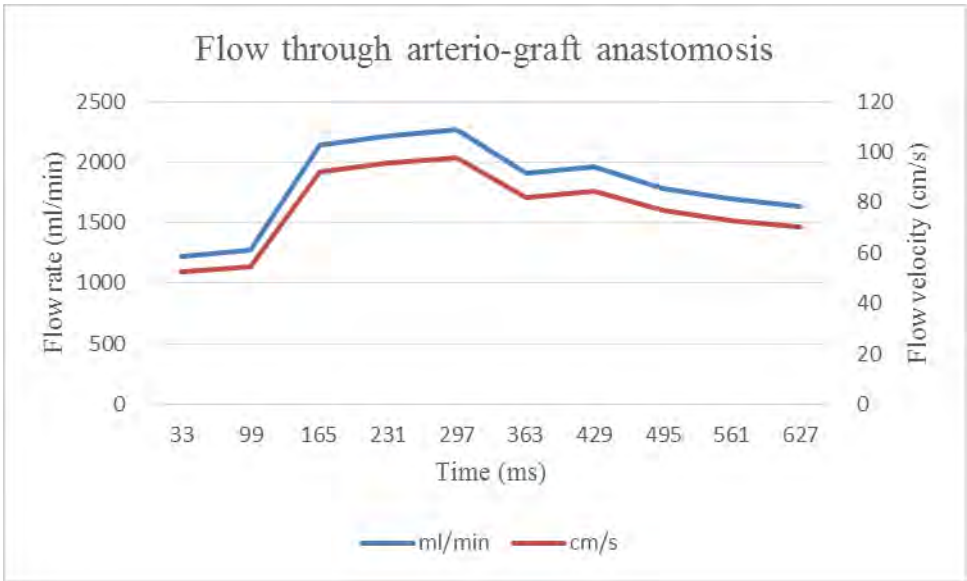


Figure 9: Flow rate and flow velocity of AVG 2 proximal artery-graft anastomosis.

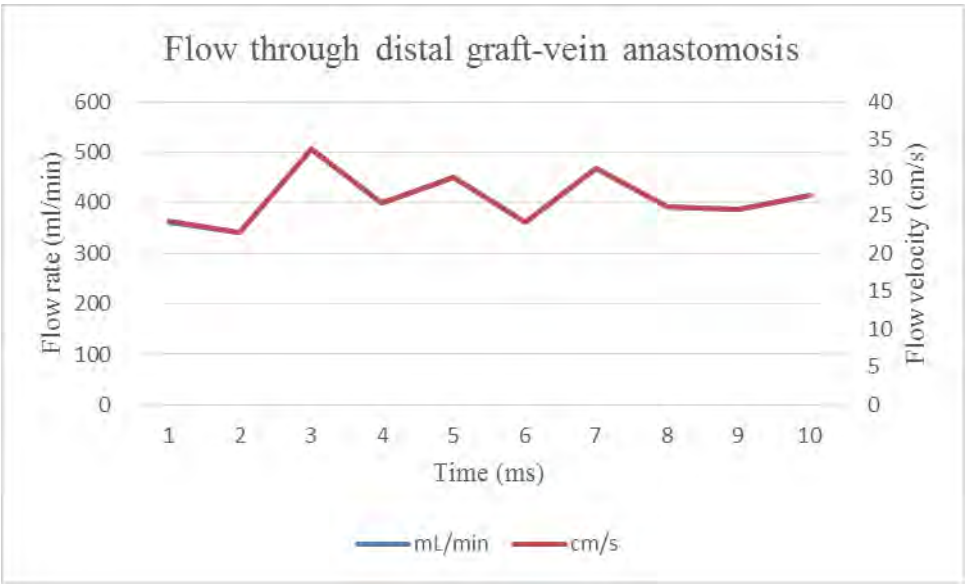


Figure 10: Flow rate and velocity of the distal graft-vein anastomosis of AVG 2.

Due to the limited results available from scanning the AVG patients, only one set of data was available for the analysis. The artery-graft anastomosis had a flow volume of 660 ml/min. and a velocity of 62 cm/sec. The flow increased proximally to 1 681 ml/min. and the velocity to 85 cm/sec. The graphs (Figures 8-11) demonstrate how different the flow versus time patterns are in each area of interest.

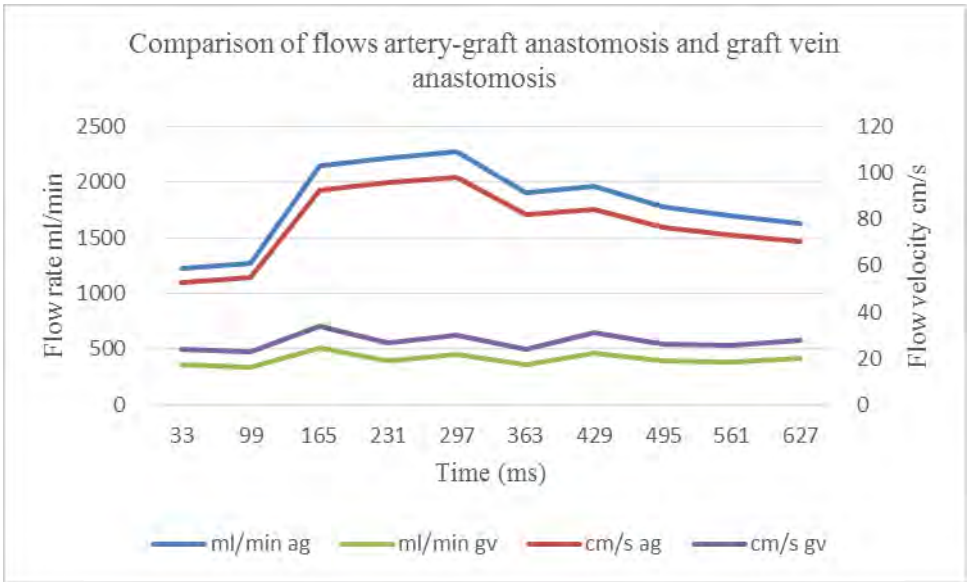


Figure 11: Comparison of flow rates and velocities through artery-graft and graft-vein anastomoses of AVG 2.

Duplex Dopplers

Peak systolic velocity (PSV) over the areas of interest scanned were recorded. PSV was fastest at the artery-graft anastomosis (307 cm/sec), and slowed through the graft to 217 cm mid-graft. All velocities recorded in AVF 5 were remarkably similar at 99.0 cm/sec to 107 cm/sec, but there was concern about the accuracy of these results.

Flow velocity

	AVF 5		**AVG 2**	
	MRI	**Duplex Doppler**	**MRI**	**Duplex Doppler**
Brachial artery	93.2	107.8	60.1	–
Arterial anastomosis	22.9	99.9	63.1	307.0
Mid-fistula/graft	24.7	99.9	–	217.0
Graft-vein anastomosis	–	–	85.0	–

Table 4: Comparison of flow velocity measured by MRI calculation and duplex Doppler.

3.4 Discussion

The aim of this study was to develop a novel imaging technique using 4D MRI technology to image dialysis access. The aim was not only to image the fistulae, but also to see whether the haemodynamic data could be used for computational modelling, which has previously been shown to generate accurate haemodynamic models of dialysis access[15]. Once the models have been built, they will be used to test various hypotheses to improve the access.

The scans on volunteers closely reflected the cardiac cycle. The later scans of dialysis patients, both the fistulae and the grafts, generated adequate 3D flow data, which allowed the generation of quantitative data of flow volumes and velocities. These studies demonstrated the complex nature and turbulence of the flows through a fistula. The access scans showed increased velocities and flow volumes through the brachial arteries as well as the access itself, in comparison to healthy volunteers. The marked increase in flow rate and velocity through the brachial arteries of the dialysis access in comparison to the healthy volunteers is thought to be due to loss of capillary network resistance in the arteriovenous access limb.

The initial access scans were limited, as flow velocities were initially vastly underestimated when determining MRI scan settings. However, as the study progressed, these settings were improved. This culminated in the complete scan of AVF 7, which not only generated 2D data, but also 4D data, and allowed full use of the 4D software, producing streamlining particle tracking images. Therefore, subsequent studies on haemodialysis access using this technique would be able to make use of the optimised 4D MRI scan protocol.

Comparison of results with currently validated imaging and velocity calculations should be interrogated further. Although 4D MRI has been validated previously on larger vessels, the added complexity of flows in arteriovenous fistulae and the fact that this was an entirely novel protocol means that further research is required. Although we attempted validation in this pilot study, it was not the primary aim of the study, and we were hampered by logistical constraints. The early lessons learnt included information about the expected velocities of flows in the vessels as well as MRI coil placement. This proved to be challenging throughout the pilot.

Coil placement was a particular challenge when scanning arteriovenous grafts, as the upper-arm coil was a standard size and did not always cover both the proximal and distal anastomoses. This also meant that central veins did not form part of the imaging. This is of clinical relevance, as a proximal stenosis is a major cause of both

failure to mature as well as access thrombosis[16]. Should this imaging technology be considered for clinical use, this problem would have to be addressed.

This was an entirely novel application of 4D MRI. Development of the scan protocol required a collaborative team effort between surgeons, imaging specialists and biomedical engineers. Presenting the data in a universally understood way was challenging. This resulted in some limitations early in the pilot, and emphasised the importance of careful and thoroughly understood communication in innovative interdisciplinary projects. Further areas of research following this pilot project should include longitudinal studies of access to assess how haemodynamics change, as the access matures over time. This would also provide valuable information for model building to allow for possible clinical changes.

3.4 Conclusion

4D flow-sensitive MRI can produce adequate quantitative data for computational model building. Further research is required to validate it in this specific clinical area, as well as refine imaging and processing.

3.5 References

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CHAPTER 4
APPENDICES

4.1 Consent form

UNIVERSITY OF
CAPE TOWN

Department of Surgery

Division of General Surgery

Prof D Kahn, MB ChM (UCT), FCS(SA)

Head of Department: Surgery – Division and Organ Transplantation

J45 Room 23, Old Main Building, Groote Schuur Hospital

Observatory, 7925, South Africa

Tel.: +27 (0)21 406 6229

Fax: +27 (0)21 448 6461

Email: Delawir.Kahn@uct.ac.za

Consent for taking part in a research study:
Imaging of haemodialysis fistulas and grafts

Why is this study being done?

This is a study that hopes to gather information about the fistula or graft in your arm that to which the needles of the haemodialysis machine are connected during your haemodialysis sessions. We hope that this will give a better understanding of why these grafts and fistulae cause problems and why they sometimes fail. We can then

use this information to try to improve fistulae or grafts, for example how long they last, and minimise the problems they cause.

Why are you being asked to participate?

You are being asked to participate because you have a fistula or graft in your arm that is used for your haemodialysis session, or we want you to take part as a healthy person for comparison.

How long will you participate in this research? How much of your time will be needed? Do you need to take time off work?

You will participate in this study for about two hours. You will not need to take time off work, as the scans will be done either on a weekday at 6 p.m. or over a weekend.

What will happen if you decide to take part in the study?

We will take images of your upper arm in the location of the graft or fistula, or your upper arm in a similar region if you belong to the group of healthy participants. The images will be taken using a magnetic resonance imaging machine. We may also take a Doppler ultrasound scan of your arm to look at your fistula or graft.

What are the risks and discomforts of this study?

The magnetic resonance imaging procedure is not painful or dangerous, and there are no known harmful long-term effects. The ultrasound Doppler procedures are not painful or dangerous and do not involve any risks. You will not require any drips, injections or medication for the scans. You may feel nervous being in the scanning machine because it is a tube-like space around you.

Are there any benefits to you for being in the study?

No, there are no benefits to you.

What other choices do you have?

Your participation is voluntary. You have the choice of not taking part in this study. Such a decision will not affect in any way your current or future medical treatment, e.g. your haemodialysis sessions.

What if something goes wrong?

The University of Cape Town (UCT) undertakes that, in the event of you suffering any significant deterioration in health or well-being, or from any unexpected sensitivity or toxicity that is caused by your participation in this study, it will provide immediate medical care. UCT has appropriate insurance cover to provide prompt payment of compensation for any trial-related injury according to the guidelines outlined by the Association of the British Pharmaceutical Industry, ABPI 1991. Broadly speaking, the ABPI guidelines recommend that the insured company (UCT), without legal commitment, should compensate you without you having to prove that UCT is at fault. An injury is considered trial-related if, and to the extent that, it is caused by study activities. You must notify the study doctor immediately of any side effects and/or injuries during the trial, whether they are research-related or other related complications.

UCT reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence will not be affected. Copies of these guidelines are available on request.

What will happen when the study is over?

Nothing will be required from you when the study is over. We will present findings of the study at conferences and in publications, for example in medical journals and in reports that students have to write.

Who can you contact or speak to if you have any questions about the study?

You can contact Associate Professor Thomas Franz (tel.: 021 406 6418; email thomas.franz@uct.ac.za), who is the principal investigator, and Dr. Jennifer Downs (tel.: 083 324 2106; email jen.s.downs@gmail.com), who will be involved in selecting the participants for this study.

If you have any questions regarding your rights or welfare as participant in this study, you can contact the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town, using the contact details below. Please mention the reference number HREC/REF454/2013.

Faculty of Health Sciences Human Research Ethics Committee

Room E52-24, Groote Schuur Hospital, Old Main Building

Observatory, 7925

Tel.: +27 (0)21 406 6492

Fax: +27 (0)21 406 6411

Email: sumayah.ariefdien@uct.ac.za

Consent

- I, the undersigned, hereby consent to taking part in the study described above. The details of the scans and study have been fully explained to me.
- I understand that participation in this study is voluntary and I am under no obligation to participate.

- I understand that no experimental device will be implanted into my body and that no tissue will be removed from my body, and no medications or contrast will be injected into my body.
- I understand that participating in this study will in no way influence my treatment nor will it have any detrimental effect on my health.
- I understand that refusing to participate in the study will not prejudice me in any way.

Patient name: _____

Patient signature: _____

Date: _____

Place: _____

Investigator name: _____

Investigator signature: _____

4.2 Patient information sheet

UNIVERSITY OF CAPE TOWN

Department of Surgery

Division of General Surgery

Prof D Kahn, MB ChM (UCT), FCS(SA)

Head of Department: Surgery – Division and Organ Transplantation

J45 Room 23, Old Main Building, Groote Schuur Hospital

Observatory, 7925, South Africa

Tel.: +27 (0)21 406 6229

Fax: +27 (0)21 448 6461

Email: Delawir.Kahn@uct.ac.za

Participant information:

Study on imaging of haemodialysis fistulae and grafts

Dear participant

Thank you for being willing to be a participant in our research. This letter will provide you with information on the study and your involvement.

Why is this study being done?

This is a study that hopes to gather information about the fistula or graft in your arm that to which the needles of the haemodialysis machine are connected during your haemodialysis sessions.

We will do a magnetic resonance imaging scan of your arm in the region of the fistula or graft, which will tell us both how this fistula or graft looks and how the blood flows inside it.

Hopefully this will allow us to better understand why these grafts and fistulae cause problems and why they sometimes fail. We can then use this information to try to improve fistulae or grafts, for example how long they last, and minimise the problems they cause.

Who are the researchers that are involved is this study?

The study is performed by a team of clinicians and researchers of the University of Cape Town and Groote Schuur Hospital – from the Department of Surgery, the Renal Unit, the Cardiovascular Research Unit, the Medical Imaging Research Unit and the Centre for Research in Computational and Applied Mechanics.

In addition, we work with two external researchers, one from the Northwestern University in Chicago, and one from Siemens Medical Solutions, the company who makes the magnetic resonance imaging (MRI) machine we will use in this study.

Data obtained from you in this study will also be used by three Masters students and one Doctoral student at the University of Cape Town in their research projects.

Why are you being asked to participate?

You are being asked to participate because you have a fistula or graft in your arm that is used for your haemodialysis session, or we want you to take part as a healthy person for comparison.

The study has participants in three groups: 1) participants with a fistula in one upper arm, 2) participants with a graft in one upper arm, and 3) participants that do not have a fistula or graft. In the participants without a graft or fistula, we will measure how the blood flows in the healthy upper arm, to find differences that a fistula or graft causes to the blood flow.

How many people will take part in the study?

Nine people will take part in this study: three with a graft, three with a fistula and three without a graft or fistula.

How long will the study last?

The entire study will last for six to 12 months, but you only need to take part once for about two hours.

What do we do to decide if you are eligible to take part?

We will get information from your hospital record, including when you received your haemodialysis graft or fistula and whether you are a candidate for a kidney transplant. If you're a participant without a haemodialysis graft or fistula, we will confirm that you do not have a history of vascular diseases and had no surgery on the upper arm.

We will check that you do not suffer of fear being in small spaces and that you do not have any medical or metal implants, such as a pacemaker for your heart.

We will also discuss with you what will happen if you participate and if you would feel comfortable with everything.

What will happen if you decide to take part in the study?

We will take images of your upper arm in the location of the graft or fistula, or your upper arm in a similar region if you belong to the group of healthy participants. The images will be taken using a magnetic resonance imaging machine. This is a tube-like machine containing a magnet in which you lie. The machine takes extremely detailed pictures of your arm and the blood vessels inside it, similar to X-ray images.

The scanning will take place in the Department of Radiology at the Groote Schuur Hospital, Ward C7. We will need 30 minutes to familiarise you with the scanner and to get you ready before your scan takes place. After that, the scanning itself will take approximately 45 minutes. We will take the images either on a weekday at 6 p.m. or on a Saturday or Sunday during the day.

At the beginning, we will ask you to change into a gown and remove metal objects, such as watches, credit cards, hairpins and writing pens before going into the scanner. The reason is that such metal objects may be damaged or pulled away from your body by the magnet.

You will then lie on a soft plastic bed that slides into the magnetic resonance imaging scanner (the tube-like machine). We will ask you to lie as still as possible while the pictures are being taken. When the scanner takes the pictures, the bed may shake slightly and you may hear loud banging noises from time to time.

We may also take a Doppler ultrasound scan of your arm to look at your fistula or graft; you may have already had one in the Renal Unit. This is a quick, painless procedure done by holding an ultrasound probe on your arm over your fistula or graft, and will also record the blood flow in the fistula or graft.

It takes approximately 15 minutes and will be done before or after the magnetic resonance imaging scan at the same location in the hospital. We would like to do this ultrasound scan so that we can compare the ultrasound scan with the magnetic resonance imaging scan.

What are the risks and discomforts of this study?

Any medical devices or pieces of metal implanted in your body or under your skin can be damaged by the scanning machine (but can also damage the scanning machine itself).

Please let us know if you, for example, have a pacemaker for your heart or a metal part that is used to fix a broken bone in the arm or leg, as you cannot participate in this study in such cases.

The magnetic resonance imaging scan requires that you lie in a narrow tube. Please also let us know if you have a fear of being in a small space.

You may feel nervous being in the scanning machine because it is a tube-like space around you.

We will give you earplugs to protect your ears and headphones so we can talk to you. You may also get a blanket so that you don't get cold during the scanning procedure. We will not start with taking images until you tell us that you are comfortable.

You will be able to stop the scan at any time by squeezing a ball that you will hold in one hand, and you can talk to us at any time during the scanning procedure using an intercom that is built into the scanner.

The magnetic resonance imaging procedure is not painful or dangerous, and there are no know harmful long-term effects. The ultrasound Doppler procedures are not painful or dangerous and do not have any a risk for you. You will not require any drips, injections or medication for the scans.

Are there any benefits to you for being in the study?

No, there are no benefits to you. There may be benefits for patients like you in the future if the study leads to improvements of haemodialysis grafts or fistulae.

What other choices do you have?

Your participation is voluntary. You have the choice of not taking part in this study. Such a decision will not affect in any way your current or future medical treatment, e.g. your haemodialysis sessions.

What if something goes wrong?

The University of Cape Town (UCT) undertakes that, in the event of you suffering any significant deterioration in health or well-being, or from any unexpected sensitivity or toxicity that is caused by your participation in the study, it will provide immediate medical care. UCT has appropriate insurance cover to provide prompt payment of compensation for any trial-related injury according to the guidelines outlined by the Association of the British Pharmaceutical Industry, ABPI 1991.

Broadly speaking, the ABPI guidelines recommend that the insured company (UCT), without legal commitment, should compensate you without you having to prove that UCT is at fault. An injury is considered trial-related if, and to the extent that, it is caused by study activities. You must notify the study doctor immediately of any side

effects and/or injuries during the trial, whether they are research-related or other related complications.

UCT reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence will not be affected. Copies of these guidelines are available on request.

What will happen when the study is over?

Nothing will be required from you when the study is over. We will present findings of the study at conferences and in publications, for example in medical journals and in reports that students have to write.

Will your test results be shared with you?

No, the results of the imaging tests will not be shared with you.

Will the results of the research be shared with you?

No, the results of the research will not be shared with you.

Will any of your blood, tissue or other samples be stored and used for research in the future?

No, we will not take or store any blood, tissue or other samples from you.

Will you receive any reward (money or food vouchers) for taking part in this study?

Yes. We will refund your costs for transport to Groote Schuur Hospital for the imaging procedures and back home up to R200. We will also give a voucher of R50 for refreshments at Groote Schuur Hospital.

Who will see the information that is collected about you during the study?

The researchers and students involved in this study will see the data obtained from you, but without your personal information. Only the principal investigator (A/Prof Thomas Franz) and the clinical registrar who is involved in your recruitment (Dr. Jennifer Downs) will see your personal information.

We will also send report and data obtained in this study without your personal information to Siemens Medical Solutions GmbH, the manufacturer of the magnetic resonance imaging machine we use in this study. This is part of a collaboration agreement that allows us to use an analysis software developed by Siemens.

Will your data be confidential?

Your personal information will be confidential and we will use pseudonyms instead of your name to recognise your data. Any personal information will be kept in a secure location.

Who can you contact or speak to if you have any questions about the study?

You can contact Associate Professor Thomas Franz (tel.: 021 406 6418; email thomas.franz@uct.ac.za), who is the principal investigator, and Dr. Jennifer Downs (tel.: 083 324 2106; email jen.s.downs@gmail.com), who will be involved in selecting the participants for this study.

If you have any questions regarding your rights or welfare as participant in this study, you can contact the Human Research Ethics Committee of the Faculty of

Health Sciences at the University of Cape Town, using the contact details below. Please mention the reference number HREC/REF454/2013.

Faculty of Health Sciences Human Research Ethics Committee

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4.3 Departmental Research Committee approval

Form D1(a): for MMed and MPhil (sub-specialty) registrars to submit with study proposal

University of Cape Town, Faculty of Health Sciences

Form D1(a): Scientific and educational validity form for specialty/subspecialty MMed/MPhil degrees (from 2015)

Study Title: Flow Velocity Measurement in Haemodialysis access using 4D Magnetic Resonance Imaging

The Synopsis is complete and presented according to UCT HREC guidelines, form FHS014.	xYes / No

Where minor changes are needed, indicate on the protocol; where major changes are needed please attach comments on a separate page

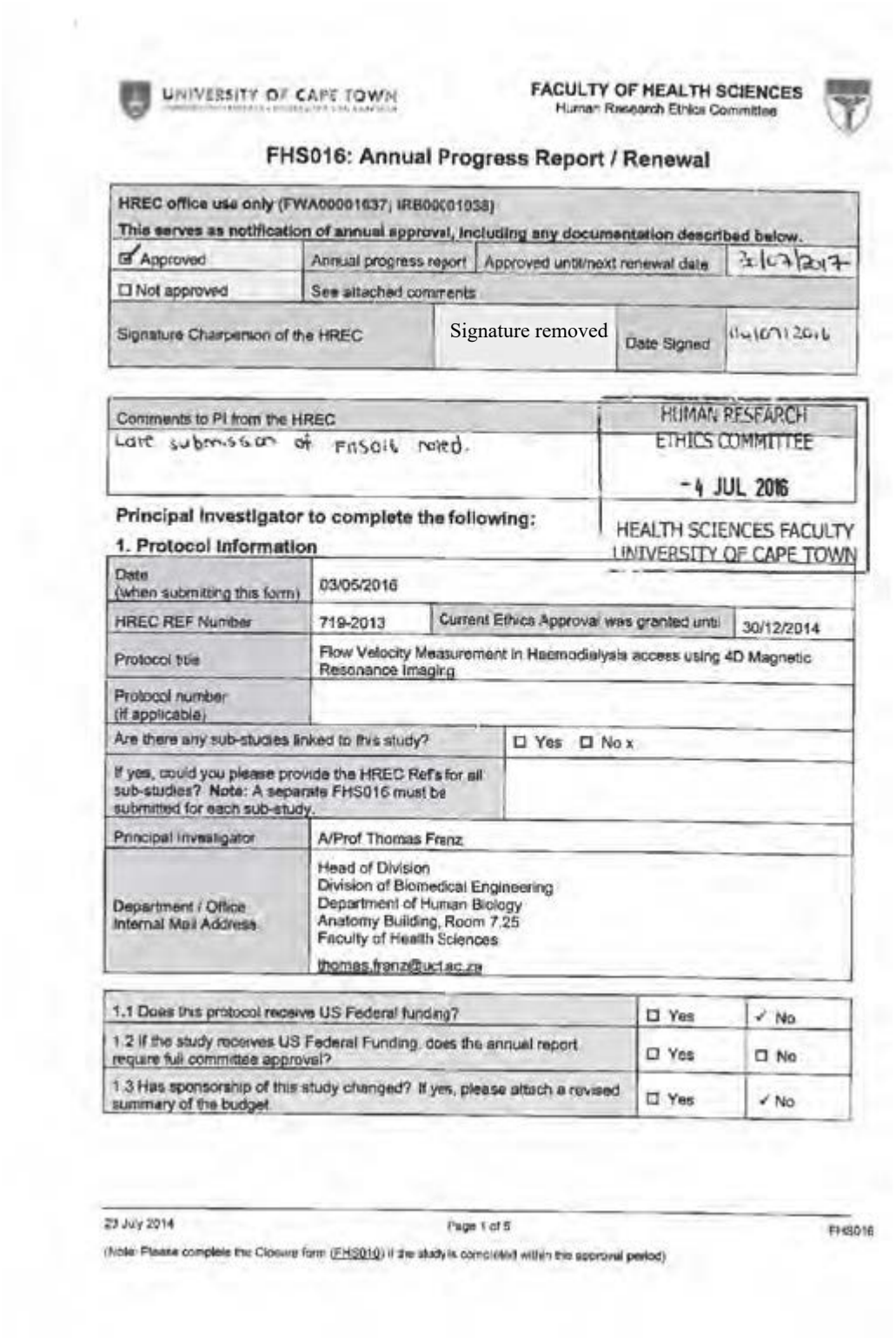
PROTOCOL	No change	Minor changes	Major Changes
1. **The purpose and background (literature review) are appropriately presented.** The setting, current practice and gaps in the literature are described to provide sufficient rationale to justify the purpose of the study and to contextualise the importance/relevance of the study			
2. **The objectives are clearly stated, linked to the purpose and are feasible within the available time and resources**			
3. **Methodology:** **a. The design is appropriate to the objectives, is feasible and is adequately funded** **b. The method is written in sufficient detail for publication purposes** **c. The sample characteristics and size are described and justified in the context of the objectives; and the recruitment/sampling method is appropriate** Studies that aim to compare one treatment/intervention/scenario with another as a primary objective have power calculations provided unless they are primarily exploratory and/or establishing baseline data for the context **d. There is a clear description of which data will be collected, by whom and how it relates to the objectives** **e. The data reporting and statistical analysis methods are appropriately described** (including: electronic programme e.g. Excel, Stata, other; appropriate tests; and probability levels/confidence boundaries (if applicable) **f. The limitations of the methodology are discussed**			
4. **The ethical considerations are clearly and appropriately described.** Research subjects assured of confidentiality, anonymity and respect. Data storage is appropriate. Possible adverse effects or risks associated with the audit outcomes described. Consent procedure is described (or lack of consent justified) and associated forms are attached. The data dissemination procedures at the end of the study and subsequent patient/situational management are described. The process of obtaining institutional, ethical and provincial approval is described.			
5. **All references are included with the same referencing format throughout.**			
6. **The literary style of writing and presentation is acceptable.**			
7. **The proposal is scientifically suitable for an MMed / MPhil in keeping with the current UCT guidelines.**			
8. **Appropriate appendices are attached.** (including consent and assent form (if appropriate); budget; and data collection forms)			

My signature below confirms that the protocol named above meets the requirements indicated above for an MMed/MPhil minor dissertation; submitted by Jennifer Downs (Registrar Name)

Signed: Signature removed **Name...Prof A Mall**

Capacity: (ring) Departmental Research Chair/Registrar review committee chair or representative

4.4 Human Research Committee approval



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FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001038) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	3/07/2017
☐ Not approved	See attached comments		
Signature Chairperson of the HREC	Signature removed	Date Signed	04/07/2016

Comments to PI from the HREC	HUMAN RESEARCH ETHICS COMMITTEE
Last submission of FHS016 noted.	- 4 JUL 2016
	HEALTH SCIENCES FACULTY UNIVERSITY OF CAPE TOWN

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	03/05/2016		
HREC REF Number	719-2013	Current Ethics Approval was granted until	30/12/2014
Protocol title	Flow Velocity Measurement in Haemodialysis access using 4D Magnetic Resonance Imaging		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☐ No x		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	A/Prof Thomas Franz		
Department / Office Internal Mail Address	Head of Division Division of Biomedical Engineering Department of Human Biology Anatomy Building, Room 7.25 Faculty of Health Sciences thomas.franz@uct.ac.za		

1.1 Does this protocol receive US Federal funding?	☐ Yes	✓ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	☐ No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget	☐ Yes	✓ No

23 July 2014 Page 1 of 5 FHS016

(Note: Please complete the Closure form (FHS010) if the study is completed within this approval period)

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

2. List of documentation for approval

3. Protocol status (tick ✓)

☐	Open to enrolment
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
✓	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	15
Number of participants enrolled, since last HREC Progress report (continuing review)	15
Additional number of participants still required	0

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	N/A

6. Cumulative summary of participants

Total number of participants who provided consent	15
Number of participants determined to be ineligible (i.e. after screening)	0
Number of participants currently active on the study	0
Number of participants completed study (without events leading to withdrawal)	15
Number of participants withdrawn at participants' request (i.e. changed their mind)	0
Number of participants withdrawn by PI due to toxicity or adverse events	0
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	0
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up	0
Number of participants no longer taking part for reasons not listed above. Please provide reasons below	0

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report, as well as any relevant comments/issues you would like to report to the HREC
This study to date has been to explore whether or not 4D MRI can generate flow velocity data in haemodialysis access using existing data analysis tools, as well as modifying and developing others. Recruitment and scanning of patients is completed, and final data analysis by the team is nearing completion. I have been involved in both recruitment and patient scanning, both MRI and Duplex Doppler, as well as review of generated data. All procedures involving patients were completed before 30 Dec 2014.

8. Protocol violations and exceptions (tick ✓ all that apply)

✓	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

☐	No prior amendments have been made since the original approval
✓	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).
Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

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FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?		
☐ Yes	☐ No	✓ Not applicable
If yes, please describe:		

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. MCC, FDA)?		
☐ Yes	☐ No	✓ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	✓ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	✓ No
If yes, please explain:	

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Human Research Ethics Committee

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
✓	Shown no change
If there has been a change, please explain	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk

13. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	✓ No
If yes, please explain and if necessary attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

14. Signature

My signature certifies that the above is complete and correct			
Signature of PI	Signature removed	Date	3 May 2016

4.5 Journal instructions

WORLD JOURNAL OF SURGERY INSTRUCTIONS FOR AUTHORS

GENERAL

World Journal of Surgery (*WJS*) publishes original articles that offer significant contributions to knowledge in the broad fields of clinical surgery, innovative developments in surgery, global surgical practice and economics, surgical education, rural surgery and surgical history. *WJS* welcomes predominantly human research, including clinical research, outcomes, and health service research. Laboratory research will be published only if it is highly significant and with clear and immediate translational potential to surgical care. *WJS* has an international circulation and is designed to serve as a medium for rapid dissemination of new and important information about the science and art of surgery throughout the world. In the interests of a wide international readership, use of the English language is required. Articles that are accepted for publication are done so with the understanding that they, or their substantive contents, have not been and will not be submitted to any other publication.

TYPES OF MANUSCRIPTS

PLEASE NOTE: *World Journal of Surgery* does not accept Case Reports and Book Reviews for review or publication. *WJS* will consider publication without prior invitation the following types of manuscripts:

Original Scientific Reports: Original Scientific Reports are full-length reports of original basic or clinical investigations. Original Scientific Reports must adhere to a 2,500 word limit (not including the title page, abstract, references, tables, and figures). The final word count should be included in the title page of the manuscript. All clinical trials must be registered through a public trials registry that is acceptable to the International Committee of Medical Journals Editors (ICMJE). For information on ICMJE's statement to register clinical trials, please go to http://www.icmje.org/publishing_10register.html. The trial registration number and agency should be listed on the title page and at the end of the abstract. Randomized clinical trials should be reported following the CONSORT criteria and provide a completed checklist and flow diagram upon manuscript submission. For information on CONSORT and to download the CONSORT checklist and flow diagram, please go to http://www.consort-statement.org/.

Brief Original Scientific Reports: Brief communications describing an original observation or new technique. All efforts will be made to expedite review and publication of noteworthy brief reports. Brief Original Scientific Reports must adhere to a 1,500 word limit (not including the title page, abstract, references, tables and figures). The final word count should be included in the title page of the manuscript.

Innovative Techniques in Surgery around the World: The WJS is interested in publishing high quality descriptions of innovative surgical techniques that have the potential to improve the quality or efficiency of care. While techniques with universal appeal are most sought after, novel techniques that allow broader access to care in resource challenged environments are also desirable. The successful manuscript will contain a detailed description of the technique and be richly illustrated with figures, and/or video. Line drawings are much superior to intraoperative photos, generally. A brief description of the authors experience with the technique should also be included, if possible. Qualifying manuscripts should be less than 1250 words, have no more than 3 authors, have no more than 5 references, and no more than 8 figures/video segments. A brief unstructured abstract is also required. Please see our instructions for submitting streaming video, below.

Papers Presented at ISW Congress: Includes manuscripts presented at an International Surgical Week (ISW) World Congress or at an Integrated Society meeting.

Multimedia Scientific Reports: *WJS* seeks manuscripts that contain brief video clips of surgical techniques or operative findings. Please see the "**MULTIMEDIA MANUSCRIPT SUBMISSION**" below for submitting video augmented manuscripts.

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Letter to the Editor: Letters should pertain to material previously published in *WJS*. Letters should not exceed 500 words with no more than five references, the first of which should be the article on which you wish to comment.

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- Editorial Perspective
- Invited Scientific Review
- Invited Symposium Papers
- Reply to Letter to the Editor
- Invited Commentary
- Surgical History

MANUSCRIPT SUBMISSION GUIDELINES AND REQUIREMENTS

All manuscripts must be submitted online to *WJS* via the ScholarOne Manuscripts website (formerly Manuscript Central). Please login directly onto the site at http://mc.manuscriptcentral.com/WJS and upload your manuscripts following the instructions given on the screen. Authors should keep copies of all manuscript files. *WJS* accepts no responsibility for files that are lost or destroyed due to electronic problems. Upon manuscript submission, the Editorial Office will review all manuscript files to verify that guidelines and policies stated in this document are adhered to. Your manuscript will be unsubmitted if it does not meet the proper submission requirements.

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MANUSCRIPT PREPARATION AND ORGANIZATION

General instructions:

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- Use italics for emphasis
- Use the automatic page numbering function to number the pages
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- Use tab stops or other commands for indents, not the space bar
- Use the table function, not spreadsheets, to make tables

Manuscript style and text formatting: Styling and text formatting refers to the use of special effects to enhance the appearance of the published article. Please make note of the following "Dos and Don'ts" regarding styling:

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- **DO NOT** use multiple spaces to set up columns or tables; use tabs instead.
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- The name(s) of the author(s) including the affiliation(s) and address(es) of each author. The complete name and address of the author to whom correspondence should be sent, as well as his/her phone number, fax number, and email address.
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- Keywords: 2-3 keywords relevant to the manuscript
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TEXT: Original Scientific Reports should be arranged in sections titled Introduction, Material and Methods, Results, and Discussion

1. Introduction: conveys the background and purpose of the report
2. Material and Methods
3. Results & Discussion

When required by the nature of the report, manuscripts that do not follow this specific format may be accepted.

ACKNOWLEDGEMENTS: A brief statement should acknowledge individuals, other than authors, who were of direct help in the reported work or if the work was supported by a federal or commercial grant. All acknowledged persons should give their written consent to being named in the manuscript. This consent is to be uploaded upon manuscript submission.

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1. Honda T, Nozaki M, Isono N, et al (2001) Endoscope-assisted facial fracture repair. World J Surg 25:1075-1083

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1. Harlan BJ, Starr A, Harwin FM, Anesthesia for cardiac surgery (1986) In: Illustrated Handbook of Cardiac Surgery, Springer-Verlag, New York, p. 6-12

2. Jones MC, Smith RB, Treatment of gastric cancer (1976) In: Ford TL (ed) Cancer of the Digestive System, Springer-Verlag, Berlin, p. 140-154

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- Identify any previously published material by giving the original source in the form of a reference at the end of the table caption
- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body

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- Supply all figures electronically
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- Vector graphics containing fonts must have the fonts embedded in the files
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- Color art is free of charge for online publication.
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- Color artwork should be submitted as RGP (8 bits per channel)

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- Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.
- Avoid effects such as shading, outline letters, etc.
- Do not include titles or captions into your illustrations

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- All figures are to be numbered using Arabic numerals.
- Figure parts should be denoted by lowercase letters (a, b, c, etc.)
- Figures should always be cited in text in consecutive numerical order.
- If an appendix appears in your manuscript and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures, "A1, A2, A3, etc." Figures in online appendices (Electronic Supplementary Material) should, however, be numbered separately.

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- Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.
- Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.
- No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.
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- Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption

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REVIEW AND ACTION

The editorial staff will examine the manuscripts and will customarily send them to appropriate experts. Authors will be notified as to the acceptability of a manuscript as rapidly as possible. All manuscripts will be put through iThenticate, an online plagiarism detection tool comparing the manuscript against previously published scientific work in other journals. If any misconduct is detected, the editorial office will contact the author(s) concerning next steps and actions.

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CONSENSUS STATEMENT ON SUBMISSION AND PUBLICATION OF MANUSCRIPTS

(Published in the June 2001 issue of *World Journal of Surgery*, page A7)

Increasing problems of duplicate and fraudulent submissions and publications have prompted the editors of surgical journals, including *World Journal of Surgery*, to support these overall principles of publication:

Duplicate Submission and Publication

In general, if a manuscript has been peer-reviewed and published, any subsequent publication is duplication. Exceptions to this general rule may be:

a) Prior publication in meeting program abstract booklets or expanded abstracts such as those published by the Surgical Forum of the American College of Surgeons or Transplantation Proceedings. However, these must be referenced in the final manuscript.

b) A manuscript which extends an original database (a good rule might be expansion by 50% or more) or which analyzes the original database in a different way in order to prove or disprove a different hypothesis. Previous manuscripts reporting the original database must, however, be referenced.

c) Manuscripts which have been published originally in non-English language journals, provided that the prior publication is clearly indicated on the English language submission and referenced in the manuscript. In some circumstances, permission to publish may need to be obtained from the non- English language journal.

For example, any submission duplicating material previously published in full in "Proceedings" or book chapters is considered duplicate unless the exceptions in (a) above apply. Similarly, manuscripts dealing with subgroups of data (i.e., patients) that have previously been analyzed, discussed and published as a larger group are considered duplicate unless (b) above applies.

The Internet raises special concerns. If data have previously appeared on the Internet, submission of those data for publication is considered duplication. If Internet publication follows journal publication, the journal publication should be clearly referenced. Some journals may provide early Internet publication of accepted peer reviewed papers which are subsequently published in that journal. This does not constitute duplication if both manuscripts are identical and covered by the same single copyright.

Fraudulent Publication

The following activities are examples of fraudulent publication practices:

a) Willful and knowing submissions of false data for publication.
b) Submission of data from sources not the author's (or authors') own.
c) Falsely certifying that the submitted work is original and has not been submitted to, or accepted by, another journal.
d) Sponsoring or vouching for a manuscript containing data over which the sponsor has no control or knowledge.
e) Allowing one's name to appear as an author without having contributed significantly to the study.
f) Adding an author's name to a manuscript to which he/she has not contributed, or reviewed or agreed to in its current form.
g) Flagrant omission of reference to the work of other investigators which established their priority.
h) Falsification of any item on the copyright form.
i) Failure to disclose potential conflict of interest with a sponsoring agency.

While not intended as an all-inclusive document, these examples and guidelines should alert authors to potential problems that should be avoided when they are considering submission of a manuscript to a peer-reviewed journal.

Surgery Journal Editors Group Consensus Statement on the Adoption of the COPE Guidelines

We, the undersigned member journals of the Surgery Journal Editors Group (SJEG), in the furtherance of integrity in surgical and scientific publication, agree to adopt the guidelines established by the Committee on Publication Ethics (COPE)[2]. The COPE guidelines represent a means of addressing a variety of ethical concerns, including duplicate publication and authorship misconduct issues, which have, unfortunately, become more prevalent.
This statement is being simultaneously published in the respective journals of the members of the Surgery Journal Editors Group, as follows:

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Layton F Rikkers, MD, Keith D Lillemoe, MD
Annals of Surgical Oncology
Charles M Balch, MD
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Surgical Laparoscopy, Endoscopy & Percutaneous Techniques
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The American Surgeon
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World Journal of Surgery

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Zentralblatt für Chirurgie
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COPE Committee on Publication Ethics

CONSENSUS STATEMENT ON SURGERY JOURNAL AUTHORSHIP – 2006

In the majority of clinical and research studies submitted to surgery journals for possible publication, many individuals participate in the conception, execution, and documentation of each of those works. However, recognition of work in the form of authorship has varied widely. This consensus statement is being issued to clarify and define the criteria for surgical journal authorship.

The following guidelines should be used to identify individuals whose work qualifies them as authors as distinct from those who are contributors to the work under consideration. All persons designated as authors should qualify for authorship, and all those who qualify should be so credited.

A. Authorship Criteria

Individuals claiming authorship should meet all of the following 3 conditions:

1. Authors make substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data;
2. Authors participate in drafting the article or revising it critically for important intellectual content; and
3. Authors give final approval of the version to be submitted and any revised version to be published.

Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Allowing one's name to appear as an author without having contributed significantly to the study or adding the name of an individual who has not contributed or who has not agreed to the work in its current form is considered a breach of appropriate authorship.

Acquisition of funding, collection of data, contributing cases, or general supervision of the research group, of itself, or just being the Chair of the department does not justify authorship if the above criteria are not fulfilled.

B. Order of Authors

The order of authorship on the byline should be a joint decision of the co-authors. Authors should be prepared to explain the order in which authors are listed.

C. Multi-Center Studies

When a large, multi-center group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above and editors will ask these individuals to complete journal-specific author and conflict of interest disclosure forms. When submitting a group-author manuscript, the corresponding author should clearly indicate the preferred citation and should clearly identify all individual authors as well as the group name.

D. Contributors Listed in Acknowledgments

All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include: individuals who allowed their clinical experience (i.e., cases) to be included, a person who provided purely technical help, writing assistance, or a department Chair who provided only general support. Financial and material support should also be acknowledged.

Groups of persons who have contributed materially to the paper but whose contributions do not justify authorship may be listed under a heading such as "clinical investigators" or "participating investigators," and their function or contribution should be described - for example, "served as scientific advisors," "critically reviewed the study proposal," "collected data," or "provided and cared for study patients."

Because readers may infer their endorsement of the data and conclusions, all persons listed as contributors must give written permission to be acknowledged.

E. In Conclusion

This consensus statement is intended as a basic guide for authors. In the interest of promoting the highest ethics in surgical publishing and the surgical sciences, we ask that authors take these criteria into careful consideration when submitting a manuscript to a peer-reviewed surgical journal. This statement is being simultaneously published in the respective journals of the members of the Surgical Journal Editors Group, as follows:

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The American Surgeon
Talmadge A. Bowden, Jr. MD
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Journal of Pediatric Surgery
Jay Grosfeld, MD
Pediatric Surgery International
Arnold G. Coran, MD, Prem Puri, MD
Journal of Pelvic Medicine and Surgery
Robert D. Moalli, MD
Journal of Plastic & Reconstructive Surgery
Rod J. Rohrich, MD
Journal of Surgical Research
David McFadden, MD, Wiley W. Souba, MD
Journal of Trauma
Basil A. Pruitt, Jr, MD
Journal of Thoracic & Cardiovascular Surgery
Mathew S. Wechsler, MD
Journal of Vascular Surgery
Mark L. Cronenwett, MD, James M. Seeger, MD
Surgery
Andrew L. Warshaw, MD, Michael Sarr, MD
Surgical Endoscopy
Bruce V. MacFadyen, Jr, MD, Alfred Cuschieri, MD
Surgical Laparoscopy, Endoscopy & Percutaneous Techniques
Maurice E. Arregui, MD, Carol Scott-Conner, MD
World Journal of Surgery
John G. Hunter, MD
Zentralblatt für Chirurgie
Hans Lippert, MD

http://www.springer.com/journal/268

World Journal of Surgery
Official Journal of the International Society of Surgery/Société Internationale de Chirurgie
Editor-in-Chief: Hunter, J.G.
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Journal no. 268

4.6 Ethics approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone (021) 406 6338 • Facsimile (021) 406 6411
Email: shanelia.thomas@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

11 December 2013

HREC REF: 719/2013

A/Prof T Franz
Surgery
Cardiovascular Research Unit
Chris Barnard Building

Dear A/Prof Franz

PROJECT TITLE: FLOW VELOCITY MEASUREMENT IN HAEMODIALYSIS ACCESS USING 4D MAGNETIC RESONANCE IMAGING

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study. We acknowledge that the student Jennifer Downs is also involved on this project for her Mmed degree.

Approval is granted for one year until the 30th December 2014

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period. (Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC reference no in all your correspondence.

Yours sincerely

Signature removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001538
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.